

Vaccinations in Children and Adolescents Treated With Immune-Modifying Biologics: Update and Current Developments



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Treatment with immune-modifying biologics has positively impacted disease control and quality of life in many patients with immune-mediated disorders. However, the higher susceptibility to common and opportunistic pathogens is of concern. Thus, immunization strategies to control vaccine-preventable diseases represent a critical issue in this population. However, limited data exist on the safety, immunogenicity, and efficacy of available vaccines in patients on biologics, particularly in children. Here, according to published literature and real-life experience and practice, we report the interim indications of the Italian Society of Pediatric Allergology and Immunology (SIAIP) Vaccine Committee and of the Italian Primary Immunodeficiency Network (IPINet) Centers on immunization of children and adolescents receiving biologics. Our aim is to provide a practical guidance for the clinician to ensure optimal protection for patients and the community. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:1485-96)

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INTRODUCTION

Over the past 2 decades, immune-modifying biologics (IMBs) have revolutionized the treatment of immune-mediated and autoinflammatory diseases, owing to their efficacy, fast action, and good tolerability. The IMBs target different components of the immune system causing various degrees of

immunosuppression that can last for weeks to several months after discontinuation. Furthermore, patients receiving IMBs have an increased risk of infectious diseases and associated complications with a significant burden of morbidity and mortality. The higher susceptibility to infections may be due to complex multifactorial interactions among the underlying immune dysfunction, comorbidities, and immunomodulating drug effects. Thus, immunization toward vaccine-preventable pathogens is a critical issue in this population. However, whether these patients can mount an adequate response to vaccines is a matter of debate. Vaccine exposure may variably induce humoral and cellular immunity. Type and duration of specific protective immunity and the relationship with disease activity, disease flares, or relapses remain unclear for most available vaccines. Indeed, long-term follow-up data are lacking and cellular immunity is not evaluated in most studies. Also, surrogate markers of efficacy, such as seroprotection and seroconversion rates, are used as primary study outcomes instead of the frequencies of infection occurrence. Future studies on vaccine efficacy in the various categories of patients receiving biologics are needed owing to current limited evidence.

In this paper, we provide a practical approach to help the clinician in the vaccine decision process for children receiving biologics based upon a review of the available literature, the real-life experience and practice of the Italian Society of Pediatric Allergology and Immunology (SIAIP) Vaccine Committee and the Italian Primary Immunodeficiency Network (IPINET) Centers.

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Abbreviations used

<i>BLyS</i> - B-lymphocyte stimulator
<i>COVID-19</i> - Coronavirus disease 2019
<i>EMA</i> - European Medicines Agency
<i>EULAR</i> - European League Against Rheumatism
<i>FDA</i> - U.S. Food and Drug Administration
<i>HBV</i> - Hepatitis B virus
<i>IBD</i> - Inflammatory bowel disease
<i>Ig</i> - Immunoglobulin
<i>IL</i> - Interleukin
<i>IMBs</i> - Immune-modifying biologics
<i>IXE</i> - Ixekizumab
<i>JAKs</i> - Janus family protein kinases
<i>JIA</i> - Juvenile idiopathic arthritis
<i>mAb</i> - Monoclonal antibody
<i>MMR</i> - Measles-mumps-rubella
<i>MTX</i> - Methotrexate
<i>PCV</i> - Pneumococcal conjugated vaccine
<i>PPV</i> - Pneumococcal polysaccharide
<i>PPV23</i> - 23-Valent pneumococcal polysaccharide vaccine
<i>PsA</i> - Psoriatic arthritis
<i>RA</i> - Rheumatoid arthritis
<i>SARS CoV-2</i> - Severe adult respiratory syndrome coronavirus 2
<i>sJIA</i> - Systemic juvenile idiopathic arthritis
<i>SLE</i> - Systemic lupus erythematosus
<i>TCZ</i> - Tocilizumab
<i>Th</i> - T helper
<i>TNF-α</i> - Tumor necrosis factor-alpha
<i>TT</i> - Tetanus toxoid

MONOCLONAL ANTIBODIES AND SELECTIVE IMMUNE SUPPRESSORS**B cell—targeting agents****Rituximab and anti-CD20 monoclonal antibody family.**

Rituximab is an anti-CD20 monoclonal antibody (mAb) that was first approved for the treatment of oncological disorders and further extended to several immunological diseases in adults and children (Table I). In recent years, many other anti-CD20 analogs (eg, ofatumumab, ocrelizumab) have been developed. With B cell—depleting anti-CD20 mAb therapy, targeting from pre-B cells to plasmablasts, except pro-B cells and immunoglobulin G (IgG)—secreting plasma cells, hypogammaglobulinemia is not usually expected and specific antibody responses should not be impaired, although these effects occur in patients with underlying immune impairment.¹ Further, anti-CD20 mAb affects not only humoral immunity but also cognate T-B cell interactions, leading to a more profound immunological dysfunction. Previously vaccinated patients have a preserved a residual humoral response to seasonal influenza, diphtheria, tetanus toxoid (TT) vaccine after receiving rituximab.^{2–4} Conversely, within the first 6 months, in anti-CD20—treated patients, the efficacy of inactivated vaccines is altered owing to perturbation of the memory B and T cell compartment. This has been demonstrated for influenza, pneumococcal polysaccharide (PPV), and pneumococcal conjugated (PCV) vaccines in adults with immune thrombocytopenia (ITP) and rheumatoid arthritis^{4–7} and for hepatitis B vaccines in patients with autoimmune disorders.⁸ The B cell recovery after anti-CD20 mAbs therapy mostly occurs within 6 to 12 months post treatment.¹ Notably, it is not possible to recommend a specific threshold of B cell count for an effective immune response to non—live vaccines because vaccine responses have

been reported to be blunted, although present, with B cell aplasia.⁹ However, because an optimal humoral response is unlikely to be obtained during the B cell—depletion phase, it is recommended to postpone inactivated vaccines for 6 to 12 months after rituximab infusion.¹⁰ No data are available for the use of live vaccines in children treated with anti-CD20 mAb. Thus, they should not be administered for at least 6 months post infusion and until B cell recovery has occurred. Because impaired humoral response could represent a risk factor for treated children, an up-to-date vaccine administration schedule is recommended to be completed at least 4 weeks prior to the first infusion.¹¹

Belimumab. Blocking B cell proliferation with no direct B cell death induction is effective in patients with severe, refractory systemic lupus erythematosus (SLE).¹² Belimumab is a humanized IgG1 mAb that targets soluble B-lymphocyte stimulator (BLyS), a crucial factor for survival and differentiation, leading to a reduction of circulating CD19+, CD20+, naive, activated B cells, and plasma cells. This mAb is currently approved for treatment of adults with SLE, but clinical trials have already explored its efficacy and safety in children.^{13,14} Limited data are available on the impact of anti-BLyS mAb on vaccine responses. Because memory B cells are usually only partially affected, vaccine responses should not be impaired. In a small randomized study, antibody titers to previous pneumococcal, TT, and influenza immunizations were not affected in patients with SLE.¹⁵ Non—live vaccines have been safely administered in patients receiving treatment with belimumab, although there are limited data on their efficacy. Humoral response to pneumococcal conjugate vaccine is similar in patients receiving either anti-BLyS mAb or other immunosuppressants such as azathioprine, hydroxychloroquine, methotrexate (MTX), and prednisolone.¹⁶ Conversely, anti-influenza immunizations resulted in a slightly increased titer.¹⁵ A randomized clinical trial showed comparable proportions of responders to 23-valent pneumococcal polysaccharide vaccine (PPV23) in patients vaccinated 4 weeks before administration of belimumab or after 6 months of treatment, and the majority of them mounted a protective immune response.¹⁷ Because no more data are available, inactivated vaccines are strongly encouraged in patients with SLE receiving IMBs, including belimumab.¹⁸ Conversely, owing to the paucity of safety data on live vaccines, they are contraindicated within 30 days before or right after administration of belimumab.^{19,20}

T cell—targeting agents**Cytotoxic T lymphocyte—associated antigen—4 pathway modifiers: abatacept.**

Selective T cell—targeting drugs have provided a new treatment route for several patients affected by severe/refractory autoimmune disorders. Abatacept represents one of these innovative agents that has been first used for treatment of rheumatoid arthritis,²¹ followed by a broader application in different immune-mediated conditions, including juvenile idiopathic arthritis and systemic sclerosis. As the result of combination between cytotoxic T lymphocyte—associated antigen 4 and the constant region of IgG1, abatacept acts as a blocker of cognate T cell—antigen—presenting cell interactions, by binding CD80/CD86 on antigen-presenting cell and preventing engagement of CD28 on T cells. A randomized study evaluated vaccine responses in healthy subjects against TT and PPV before and after a single administration of abatacept. Although overall

TABLE I. Monoclonal antibodies and selective immune suppressors

IMBs target	Immunization prior to IMBs treatment	Immunization during IMBs treatment		Vaccine efficacy		Vaccine safety	
		Inactivated vaccine	Live vaccine	Inactivated vaccine	Live vaccine	Inactivated vaccine	Live vaccine
TNF- α Etanercept Infliximab Adalimumab Certolizumab pegol Golimumab	Contrasting literature data for non—live vaccine Preserved seroprotection rate but accelerated antibody loss for live vaccine	R*	NR†	Adequate seroprotection rate but lower antibody production compared with healthy controls and patients treated without anti—TNF- α	Booster doses are efficacious‡	No serious adverse events No disease deterioration	Booster doses are safe
IL-6							
TCZ	No data	R	NR	Proven efficacy for influenza, PPV23,§ PCV7, TT	No data	No severe adverse events No disease relapse	No data
Sarilumab	No data	No data	No data	No data	No data	No data	No data
Siltuxumab	No data	No data	No data	No data	No data	No data	No data
IL-17							
Secukinumab	No data	R	NR	Proven efficacy for influenza, Men-C	No data	No severe adverse events	No data
Ixekizumab	No data	No data	No data	Proven efficacy for PPV23, TT	No data	No disease relapse	No data
Brodalumab	No data	No data	No data	No data	No data	No data	No data
IL-12, -23							
Ustekinumab	No data	R	NR	Proven efficacy for influenza, PPV23	No data	No severe adverse events¶	No data
Guselkumab	No data	No data	No data	No data	No data	No data	No data
IL-1							
Canakinumab	No data	R	NR	Proven efficacy for influenza, Men-C	No data	No severe adverse events	No data
Anakinra	No data	R	NR	Proven efficacy for TT	No data	No data	No data
IL-4							
Dupilumab	No data	R	NR	Proven efficacy for TT, meningococcal vaccines	No data	No severe adverse events	No data
IL-5							
Mepolizumab	No data	No data	No data	No data	No data	No data	No data
Benralizumab	No data	No data	No data	Proven efficacy for influenza	No data	No data	No data
Reslizumab	No data	No data	No data	No data	No data	No data	No data
CD20							

(continued)

TABLE I. (Continued)

IMBs target	Immunization prior to IMBs treatment	Immunization during IMBs treatment		Vaccine efficacy		Vaccine safety	
		Inactivated vaccine	Live vaccine	Inactivated vaccine	Live vaccine	Inactivated vaccine	Live vaccine
Rituximab#	Preserved humoral immunity	R**	NR††	Altered efficacy within the first 6 mo after treatment (influenza, PPV, PCV, HBV)	No data	Safe	No data
BLyS							
Belimumab	Preserved humoral immunity	R	NR	Proven efficacy for PCV13/PPV23, TT, influenza	No data	Safe	No data
CTLA-4							
Abatacept‡‡	Preserved humoral immunity	R§§	NR	Proven efficacy for TT, PPV, influenza	No data	Safe	No data
CD52							
Alemtuzumab	Preserved humoral immunity	R**	NR††, ¶¶	Proven efficacy for PPV23, TT, diphtheria, polio, Hib, Men-C	No data	Safe	No data
C5							
Eculizumab##	No data	R	R	Effective	Effective	Safe	Safe

BLyS, B-lymphocyte stimulator; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; NR, not recommended; R, recommended.

*To ensure adequate immune responses, the EULAR task force advises considering measuring pathogen-specific antibodies after vaccination. Prior to starting TNF- α inhibitors, it is important to check that patients are negative for HBV infection; HBV-seronegative patients should receive the 3-dose series vaccine. Yearly influenza vaccine (non-live flu vaccine) is recommended.

†It is recommended that live vaccines be administered and updated before starting anti-TNF- α . Do not give immunosuppressive drugs 3 mo before and 6 wk after (or 2–4 wk after; or 4 wk after VZV vaccine and 6 wk after MMR, depending on the different recommendations) the administration of live virus vaccines. Before starting biologic drugs, assessing VZV (and measles infection and vaccination history is recommended. If these data are unclear or there is no documentation, titers should be checked. In nonimmune patients, VZV vaccine should be considered, ideally before initiation of immunosuppressive therapy. Live vaccines can be considered on case-to-case basis during anti-TNF- α therapy (especially VZV vaccination). Prior to starting TNF- α inhibitors, it is important to check that patients are negative for tuberculosis infection.

‡A simple immunological-based checklist can be useful to evaluate immunological reactivity prior to immunization (especially for VZV).

§In combination with MTX, antibody response may be reduced.

||Only a case report exacerbation of sJIA after flu vaccine.

¶Only a higher incidence of mild injection site reactions has been found.

#Optimization of vaccine status ahead of therapy with anti-CD-20 mAbs with up-to-date schedule of administration is recommended and should be completed at least 4 wk prior to the first infusion.

**At least after 6 mo from the last dose because efficacy might be poor.

††Until lymphocyte immune reconstitution occurs and not before 6 mo after treatment.

‡‡The immunization history should be checked before starting abatacept therapy. The American College of Rheumatology recommends that patients should be brought up-to-date with immunization prior to starting treatment.

§§Response might be blunted.

|||Until at least 3 mo after treatment.

¶¶Screening of patients is recommended ahead of planned alemtuzumab infusion and offering VZV at least 6 wk before starting treatment.

##To reduce the risk of severe meningococcal sepsis, the Advisory Committee on Immunization Practices and EMA recommend planning immunization with Meningococcal ACWY at least 2–4 wk before starting treatment with eculizumab. Also Meningococcal B, haemophilus influenzae B, and antipneumococcal vaccinations are recommended prior to starting eculizumab.

responses were impaired by treatment with abatacept, the majority of patients mounted a protective immune response.²² Vaccine responses were mostly affected when vaccines were administered within 2 weeks after treatment with abatacept, whereas the patients who were vaccinated before treatment reached higher specific antibody titers than those who received vaccination after abatacept. However, immunological studies in patients with rheumatoid arthritis (RA), receiving a combination of disease-modifying antirheumatic drugs, reported variable effects of inactivated vaccines. Some authors reported blunted immunization response to seasonal influenza,^{6,23} whereas others observed protective titers for both influenza and PPV, as in healthy subjects.^{24,25} Notably, opsonization activity has not been correlated with the level of IgG response and appeared not to be affected, suggesting that RA patients can benefit from vaccinations in spite of the decrease in quantitative humoral response.²⁵ For these reasons, non-live vaccine should be offered to patients receiving treatment with abatacept as per vaccine schedule.²⁶ The immunization history should be checked before starting abatacept therapy, and the American College of Rheumatology recommends that patients should be updated with immunizations prior to starting treatment. Because no data are available for live vaccine, these are contraindicated for patients on treatment with or within 3 months of discontinuation of abatacept.²⁷

Alemtuzumab. Monoclonal antibodies leading to profound lymphocyte depletion can be adopted for the treatment of severe, refractory autoimmune disorders. The humanized IgG1 mAb anti-CD52 alemtuzumab was initially approved for treatment of oncological disorders, but it is now used in a broader spectrum of immune-mediated diseases^{28,29} and for prophylaxis of graft-versus-host disease in patients receiving allogeneic stem cell transplantation. Because CD52 is expressed on most mature lymphocytes, natural killer cells, monocytes/macrophages, epithelial cells, and thymocytes, alemtuzumab results in profound neutropenia and lymphopenia, up to 1 year after treatment discontinuation, and associated with a substantial risk of opportunistic infections for several months.³⁰ A case-control study suggested that memory humoral responses are preserved after treatment with alemtuzumab, and antigen challenges lead to adequate vaccine response to PPV23-valent, TT, diphtheria, polio, haemophilus influenzae B, and conjugated meningococcus C vaccines from 6 months after treatment discontinuation.³¹ Inactivated vaccines are safe in patients receiving alemtuzumab for immune-mediated disorders. However, these inactivated vaccines should be planned at least 6 months after treatment to reduce the risk of poor responses when administered early after treatment. Conversely, no data are available for live vaccines, and these are contraindicated at least within the first 6 months after treatment or immune reconstitution has occurred.³² Screening patients ahead of planned infusion and offering anti-varicella-zoster virus (VZV) vaccination at least 6 weeks are recommended before treatment starts.^{33,34}

Complement component blockers

Complement inhibitors have entered in clinical practice for treatment of hematological conditions triggered by an uncontrolled and/or exuberant complement activation (eg, paroxysmal nocturnal hemoglobinuria, atypical hemolytic-uremic syndrome, complement-associated thrombotic microangiopathy).³⁵⁻³⁷ Eculizumab was the first humanized mAb approved for treatment of

transfusion-dependent paroxysmal nocturnal hemoglobinuria in adults and children. By targeting the human complement protein C5, eculizumab inhibits the formation of pro-inflammatory, pro-thrombotic C5a with subsequent inhibition of assembly of the membrane attack complex. Because only the terminal complement system is blocked, the proximal cascade, responsible for opsonization of microorganisms and clearance of immune complexes, remains functional. However, as for patients with genetic dysfunction of C5,³⁸ blocking terminal complement activity and membrane attack complex formation increases patients' susceptibility to *Neisseria* spp. infections. Indeed, both clinical trials and case reports showed a notably higher risk of severe meningococcal sepsis in patients treated with eculizumab.³⁹⁻⁴¹ For this reason, the Advisory Committee on Immunization Practices and European Medicines Agency (EMA) recommends planning immunization with a tetravalent meningococcal ACWY vaccine at least 2 to 4 weeks before patients start treatment with eculizumab.⁴² Conjugated vaccines that can provide a higher immunogenic effect are preferable. Two initial doses with an interval of at least 8 to 12 weeks are recommended. Booster doses should be given every 5 years in long-term-treated patients. Similarly, anti-Meningococcal B vaccination, administered in 2 monthly doses, is also recommended.⁴³ It is noteworthy that cases of invasive meningococcal infections have been reported despite previous vaccination, mainly due to infection from different serogroups or low antibody titers.⁴¹ Although the risk of other encapsulated bacterial infection is not as noticeable as for *Neisseria* spp., antipneumococcal and anti-haemophilus influenzae B vaccination are also recommended before starting eculizumab. The U.S. Food and Drug Administration (FDA) recommends keeping updated all other vaccinations while on treatment with eculizumab.⁴⁴ Recommendations on inactivated and live vaccines for patients with genetic or secondary complement deficiencies can be applied to eculizumab-treated subjects; all vaccines are considered safe and sufficiently effective to justify administration.⁴⁵

Tumor necrosis factor-alpha inhibitors

Tumor necrosis factor-alpha (TNF- α) is a pro-inflammatory cytokine produced by activated macrophages and T lymphocytes involved in macrophage and phagocyte activation, differentiation of monocytes into macrophages, phagocyte recruitment in granuloma formation, and maintenance of granuloma integrity.⁴⁶ The dysregulation of this cytokine plays a significant role in the pathogenesis of several immune-mediated inflammatory diseases such as juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis, Crohn disease, ulcerative colitis, and plaque psoriasis. The TNF agents are also used off-label to treat steroid-refractory graft-versus-host disease and other serious immune-mediated conditions (eg, Kawasaki disease).⁴⁷ The approved TNF- α blockers that differ in their structures, pharmacokinetics, and mechanism of action are etanercept (a soluble p75 TNF- α receptor/IgG-Fc fusion protein), infliximab (a chimeric mouse/human anti-TNF- α antibody), adalimumab (a fully human monoclonal anti-TNF- α antibody), certolizumab pegol (an antigen-binding fragment [Fab'] of a humanized mAb coupled to polyethylene glycol) and golimumab (a human anti-TNF- α mAb).⁴⁸

Inactivated vaccines. According to European League Against Rheumatism (EULAR) recommendations, non-live

vaccines can be administered to pediatric patients with rheumatic diseases using anti-TNF- α therapy, as required by national vaccine guidelines.⁴⁹ All inactivated vaccines should be administered in patients with inflammatory bowel diseases (IBD) regardless of immunosuppressive therapy, as recommended by the Infectious Disease Society of America (IDSA) and the American Academy of Pediatrics.^{33,50-53} Most studies support the safety and immunogenicity of inactivated vaccines, especially in patients with low disease activity. In pediatric rheumatic diseases, non-live vaccines were found to be safe during TNF- α blocker treatment because serious adverse events or disease deterioration were not observed. Although several studies proved that TNF- α inhibitors did not reduce specific antibody rates in those patients who were vaccinated during treatment, some authors found lower antibody production to PPV23, some serotypes of PCV7 (heptavalent PCV), influenza, meningococcal C and hepatitis A vaccinations compared with healthy subjects or patients treated with other than TNF- α blockers.^{49,50,54,55} To ensure adequate immune responses, the EULAR task force advises considering measuring post-vaccine antibody titers in patients on anti-TNF- α therapy. Prior to starting TNF- α inhibitors, hepatitis B virus (HBV) status should be checked to avoid the risk of serious viral hepatitis and/or liver failure due to reactivation of latent or untreated chronic HBV infection. All HBV-seronegative patients should receive the vaccine cycle and recheck titers 1 month after completion. Patients who do not mount a protective response should be revaccinated following the standard HBV vaccine regimen (at months 0, 1, and 4 to 6) or an accelerated schedule (months 0, 1, and 2).⁵⁰ According to a recent review, previously vaccinated adolescents with IBD, in which anti-HBV is not detectable, should receive a second 3-dose and/or a single high-concentration HBV vaccine (dose 40 μ /mL) before rechecking antibody titers.⁵¹ A prospective study of 100 children and young adults previously vaccinated against HBV and treated with infliximab for IBD showed that infliximab dose, frequency of administration, and duration of therapy as well as concomitant use of other immunomodulators did not affect duration of antibody response. Conversely, patients with a higher number of infliximab administration did not mount a protective response to HBV booster dose.⁵⁶ Other studies demonstrated that anti-TNF- α agents increase the risk of loss of immune response several months post vaccination.⁵⁷ A Swedish retrospective cross-sectional study showed that children with rheumatic disease treated with MTX and anti-TNF- α therapy (etanercept, infliximab, adalimumab, and golimumab) for greater than 3 months are at risk of low-specific IgG after tetanus vaccine, while they have an intact mature B cell compartment should they receive a booster.⁵⁸ Treatment with anti-TNF- α may also induce accelerated post-meningococcal C vaccine antibody waning, with the need of revaccination.⁵⁴ Owing to increased risk of pneumonia and upper respiratory tract infections in pediatric patients on immunosuppressive therapies, pneumococcal and influenza vaccines are particularly recommended.⁵¹ According to EULAR recommendations, annual non-live influenza vaccine should be considered in all pediatric patients with rheumatic diseases. Yearly influenza vaccine is also recommended in children with IBD on immunosuppressive therapy. Although most literature data show influenza vaccine safety and immunogenicity in children with rheumatic disease, Dell'Era et al⁵⁹ showed a reduced immune response in children with JIA treated with etanercept compared with patients treated

with conventional disease-modifying antirheumatic drugs and healthy controls.^{49,60} A recent randomized study of patients with IBD on maintenance infliximab therapy showed that the administration time of influenza vaccine in relation to infliximab infusion did not affect the achievement of serological protection.⁶¹ Thus, this suggests that influenza vaccine may be administered at any time during infliximab schedule.⁶¹ According to a study on adult patients with RA and ankylosing spondylitis, administration of influenza vaccine on the same day of infliximab infusion seems to improve humoral response more than vaccination 3 weeks later.⁶² A multicenter, prospective controlled trial on 138 children and adolescents with IBD (34 patients not on immunosuppressive drugs, 55 on thiopurines, 20 on thiopurines and anti-TNF- α agents in particular infliximab or adalimumab, and 29 healthy controls) demonstrated safety and immunogenicity of booster pertussis vaccine, irrespective of treatment type.⁶³ According to local epidemiology, adhering to national vaccine guidelines also for vaccinations against cholera, Japanese encephalitis, rabies, tick-borne encephalitis, and typhoid fever, even though data are scarce, are recommended especially in patients treated with anti-TNF- α .

Live-attenuated vaccines. The EULAR task force recommends that pediatric patients with rheumatic diseases and IBD should receive live-attenuated vaccines 3 months before and 6 weeks after immunosuppressive therapy. A prospective controlled study in children with enthesitis-related arthritis on adalimumab treatment showed that fully vaccinated patients maintained satisfactory seroprotection rates against measles and rubella at 1 and 3 years after starting TNF- α blockers.⁶⁴ Combined treatment with MTX or sulfasalazine did not affect seroprotection rates. Nonetheless, the authors detected accelerated measles and rubella antibody loss related to longer duration (>3 years) of anti-TNF- α treatment. Rubella and measles-specific IgG concentrations were not affected by age, gender, high disease activity at diagnosis, time interval between the 2 measles-mumps-rubella (MMR) vaccine doses as well as time lapse from the last MMR vaccination to the beginning of adalimumab.⁶⁴ The aforementioned Swedish study found that children with rheumatic diseases treated with MTX and anti-TNF- α for at least 3 months, who only received 1 dose of MMR vaccine, had lower levels of measles-specific memory B cells than healthy controls.⁵⁸ Conversely, specific memory B cells were preserved after a booster dose administered before inclusion in the study.⁵⁸ Studies on MMR booster doses in JIA treated with biological agents (in particular, etanercept) showed no increase in disease activity or anti-inflammatory medication use within 6 months after MMR. Furthermore, etanercept given simultaneously with revaccination did not interfere with the generation of long-lived virus-restricted T cells or protective levels of virus-specific IgG antibodies.⁵⁴ Also, immunogenicity of yellow fever virus booster vaccine was observed in patients on TNF- α -blocking agents, although reduced responses were registered.^{49,65} Long-term safety of VZV vaccine was reported in 6 children with JIA treated with biologics (3 etanercept, 2 tocilizumab, 1 infliximab), although adequate protection against VZV infection was not always provided because 1 patient got mild varicella 4 months after the second vaccine dose.⁶⁶ Another study confirmed safety of VZV vaccine.⁶⁷ In a cohort of 23 pediatric rheumatic disease patients receiving immunosuppressive therapy (ie, adalimumab, etanercept, and infliximab), who were at risk for serious

chickenpox, the monovalent VZV vaccine was well-tolerated and immunogenic.⁶⁸ Serious VZV infections are the major concerns especially in immunocompromised patients receiving TNF- α inhibitors; therefore, these patients should be screened for this virus before commencement of these biologics and VZV vaccination should be individually considered based on local epidemiology for the risk of VZV exposure.^{33,49,51}

Lee et al⁶⁹ investigated 38 acute Kawasaki disease patients, aged younger than 18 months or between 4 and 6 years, who received infliximab within 90 days of MMR, VZV, or rotavirus vaccinations. No patients had adverse events or any serious infections over a 3-month period after infliximab administration.⁶⁹

A French nationwide population-based cohort study on children born to mothers with IBD and exposed antenatally to anti-TNF- α agents showed no bacilli Calmette-Guérin-related severe adverse events, including disseminated bacilli Calmette-Guérin infection, in children vaccinated before 6 months of life.⁷⁰ Pediatric patients with immune-mediated inflammatory diseases, particularly JIA and IBD, safely tolerate inactivated vaccines with no evidence of relevant worsening of the underlying disease. Although anti-TNF- α agents may reduce vaccine responses compared with controls, particularly to pneumococcal conjugate, influenza, meningococcal C, and hepatitis A vaccines, the majority of patients are able to achieve protective levels of specific antibodies.^{54,71} In addition, antibody levels seem to decline more rapidly over time in patients using anti-TNF- α drugs, raising the risk of a quicker decrease in seroprotection rate. Thus, monitoring antibody levels and additional booster vaccine doses should be considered in order to ensure adequate immune protection. Concerning live-attenuated vaccines, the evidence is scarce, but no episodes of overt disease were reported.

Interleukin inhibitors

Interleukin-6 inhibitors. Interleukin-6 (IL-6) is a cytokine with pleiotropic physiological effects on immune and inflammatory responses, on hematopoiesis and bone metabolism, as well as on neuronal and cardiovascular system development.⁷² As to the immune activities, IL-6 is involved in the B cell differentiation process, in the proliferation of T cells, and in the differentiation of cytotoxic T cells, taking part in the defense mechanisms against pathogens. Anti-IL-6 family inhibitors, including anti-IL-6R α chain (IL-6R α) and anti-IL-6 itself, represent one of the accepted treatments for several autoimmune and inflammatory conditions including RA, Castleman disease, and giant cell arteritis.⁷² Tocilizumab (TCZ) is a humanized anti-IL-6 receptor (IL-6R) mAb accepted for several diseases such as RA, Castleman disease, polyarticular and systemic juvenile idiopathic arthritis (sJIA), giant cell arteritis, and the chimeric antigen receptor T cell therapy-induced cytokine release syndrome.⁷³ Off-label TCZ efficacy has also been studied in other immune-mediated diseases such as systemic sclerosis⁷⁴ and in coronavirus disease 2019 (COVID-19) pneumonia as recently reported.⁷⁵

The impact of TCZ on influenza and pneumococcal vaccine responses has been investigated in only a few studies.^{6,76-80} No impairment of humoral immune response following both influenza and PPV23 in 28 RA patients treated with TCZ has been reported.⁷⁶ Two larger studies demonstrated the efficacy of flu and PPV23 vaccines in 2 cohorts of 194 and 190 RA patients, respectively, whereas a reduction of PPV23 antibody response has been detected in the group treated with a combination of

TCZ and MTX,^{77,78} similar to what was observed after MTX therapy with other biological drugs.⁸¹⁻⁸⁴ Of note, response to PCV7 was not affected during TCZ treatment, unlike what occurs during rituximab (anti-CD20) and abatacept (cytotoxic T lymphocyte-associated antigen 4 pathway modifier) therapies.⁶ Moreover, the influenza vaccine demonstrated a comparable efficacy with healthy controls in a cohort of 27 patients with sJIA treated with TCZ, regardless of treatment duration.⁷⁹ Lastly, a randomized controlled trial showed a nonsignificant reduction of response to PPV23 and TT vaccines in patients treated with TCZ in the short term.⁸⁰ Only, in a case report, an exacerbation of sJIA after influenza vaccine was reported.⁸⁵ Despite limited data, inactivated vaccines such as influenza, pneumococcal, and tetanus vaccines seem to be effectively and safely administrable in patients treated with TCZ. On the contrary, owing to the lack of efficacy and safety data, live-attenuated vaccines should be avoided during IL-6 inhibitors therapy, including TCZ. No data on vaccine efficacy and safety are available in patients treated with sarilumab (anti-IL-6R α) and siltuximab (antisoluble and membrane-bound IL-6R α).

Interleukin-17 axis

Interleukin 17 inhibitors. Interleukin-17 cytokine is involved in the immune response and clearance of both extracellular and intracellular pathogens.⁸⁶ Interleukin-17 induces innate-like, acute immune responses mediated by myeloid cells, stimulating the production of CXCL1, CXCL2, and CXCL8 chemokines and of IL-6 and granulocyte colony-stimulating factor.⁸⁷ Despite its important role in response to infection, IL-17 pro-inflammatory effects also have a crucial impact on the pathogenesis of several autoimmune/inflammatory disorders, such as psoriasis and PsA.⁸⁷ Secukinumab is a human anti-IL-17A mAb approved for the treatment of plaque psoriasis, PsA, ankylosing spondylitis and nonradiographic axial spondylarthritis.⁸⁸ Little data are available about vaccine efficacy and safety during treatment with secukinumab. Humoral immune response to influenza vaccine of 32 PsA patients treated for more than 3 months was found similar to healthy controls.⁸⁹ An open-label randomized study on 50 healthy volunteers immunized with influenza vaccine and conjugate group C meningococcal vaccine, in which 25 received a single injection of 150 mg secukinumab and 25 no treatment, showed that secukinumab does not interfere with the efficacy and humoral immune response to either vaccine.⁹⁰ Ixekizumab (IXE) is a humanized anti-IL-17A mAb approved for the treatment of moderate-to-severe psoriasis in adults. The only data about vaccine efficacy during IXE treatment derive from a randomized, open-label, parallel-group study conducted on 41 healthy individuals.⁹¹ These volunteers received tetanus and pneumococcal vaccines in combination with 160 mg of IXE 2 weeks prior to vaccination and 80 mg on the day of vaccination. The humoral immune response was not affected by IXE administration compared with the control group, and the vaccines were well tolerated.⁹¹ No severe adverse events nor disease relapse has been reported following vaccination.

Despite limited data, non-live vaccines such as pneumococcal, C meningococcal, and influenza seem to be safe and effective in patients treated with secukinumab and IXE, whereas no data on live-attenuated vaccines are available. There are no studies on vaccine efficacy and safety in patients treated with brodalumab, a human anti-IL-17 receptor A (IL-17RA) approved for the treatment of plaque psoriasis.

Interleukin 12- and -23 inhibitors. Interleukin-23 cytokine, produced by antigen-presenting Langerhans cells, dendritic cells, and monocytes/macrophages due to inflammatory or biochemical damage of barrier sites (ie, skin, gut, and entheses), increases number and activity of T helper 17 (Th17) cells, enhancing IL-17 production.⁹² Blocking IL-23 signaling allows a downregulation of Th17 cell function with a decrease of circulating IL-17A.⁹² Ustekinumab is a human anti-IL-12 and -23 mAb approved for the treatment of plaque psoriasis (in both adults and children), PsA, Crohn disease, and ulcerative colitis. Ustekinumab is responsible for the downregulation of both Th1 and Th17 cells development as well as T follicular helper cell generation. The T follicular helper cells are crucial for cognate T-B cell interactions to generate high-affinity antibodies.^{93,94} In a recent study, trivalent influenza vaccine humoral and cellular immune responses in 15 Crohn disease adult patients treated with ustekinumab versus 12 treated with adalimumab and 20 healthy controls was investigated.⁹⁵ No detrimental effects on immune response to influenza vaccine was found in accordance with a previous study on 60 patients with psoriasis receiving ustekinumab and immunized with PPV.⁹⁶ Also, a higher antibody response to HBV in patients treated with ustekinumab versus adalimumab and infliximab has been demonstrated.⁹⁷ Despite limited data, influenza and pneumococcal inactivated vaccines seem to be safe and effective in patients treated with ustekinumab. Conversely, live-attenuated vaccines should be avoided in these patients as well as in household members.⁹⁸ No data on vaccine efficacy and safety are available in patients treated with guselkumab, an anti-IL-23 mAb approved for the adult treatment of moderate-to-severe plaque psoriasis.

Interleukin 1 inhibitors. Interleukin-1 α and IL-1 β represent the major components of the IL-1 family and play a key role in the inflammatory response, with strong pro-inflammatory actions. Both IL-1 α and IL-1 β bind IL-1R and IL-1RAcP, activate nuclear factor- κ B transcription with consequent neutrophil recruitment and pro-inflammatory mediator production. Anakinra is an IL-1 recombinant nonglycosylated receptor antagonist targeting IL-1 receptor I (IL1RI) which impairs both IL-1 α and IL-1 β functions. It is approved for the treatment of cryopyrin-associated periodic syndromes and RA.⁹⁹ Canakinumab is a human anti-IL-1 β mAb approved in patients older than 2 years by the EMA for the treatment of cryopyrin-associated periodic syndromes tumor necrosis factor receptor-associated periodic syndrome, hyper-IgD syndrome/mevalonate kinase deficiency, familial Mediterranean fever, as well as for adult-onset Still disease and refractory sJIA.⁴³ Data on vaccine efficacy and safety during treatment with IL-1 inhibitors are extremely poor. No difference in antibody response to TT vaccine has been found in a placebo-controlled trial on 126 patients treated with anakinra.⁹⁹ In an open-label, parallel-group, randomized, single-center study on healthy subjects exposed to a single dose of 300 mg of subcutaneous canakinumab, no impairment of antibody responses to nonadjuvanted influenza and serogroup C meningococcal conjugate vaccines and no severe adverse events were reported.¹⁰⁰ Live-attenuated vaccines are not recommended for lack of data.

Interleukin-4/IL-13 inhibitors. Interleukin-4 and IL-13 are Th2 cytokines that play a key role in the pathogenesis of allergic disorders. By binding IL-4 receptor (IL-4R), IL-4 and IL-13

trigger the activation of receptor subunit-associated Janus family protein kinases (JAKs), including JAK1, JAK3, and JAK2 and, consequently, of signal transducer and activator of transcription 6 signaling pathway which enhances allergic inflammation.¹⁰¹ Dupilumab is a human IgG4 anti-IL4 receptor α (IL-4R α) mAb acting through the inhibition of both IL-4 and IL-13 signaling. Dupilumab has recently been approved in patients 6 years of age or older for the treatment of moderate-to-severe atopic dermatitis unresponsive to other treatments and as an add-on maintenance treatment in patients with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid-dependent asthma. Data on vaccine efficacy and safety during dupilumab treatment are limited. A recent study conducted on adults with moderate-to-severe atopic dermatitis treated with dupilumab did not impair humoral immune responses to tetanus and meningococcal vaccines as well as no major vaccine adverse events.¹⁰² Owing to the lack of safety and efficacy data, live-attenuated vaccines should be avoided during dupilumab treatment.

Interleukin 5 inhibitors. Interleukin-5, also known as eosinophil differentiation factor, is a cytokine with a crucial role in eosinophil growth and differentiation and in the pathogenesis of allergy and eosinophil-mediated conditions.⁴³ Mepolizumab is a humanized IgG1 anti-IL-5 mAb, approved by the FDA and the EMA as an add-on therapy for severe refractory eosinophilic asthma and by the FDA in adults with chronic rhinosinusitis with nasal polyps. Several off-label uses have been described, including different eosinophil-mediated conditions such as eosinophilic granulomatosis with polyangiitis, chronic obstructive pulmonary disease with an eosinophilic phenotype, allergic bronchopulmonary aspergillosis, primary hypereosinophilic syndrome, atopic dermatitis, or eosinophilic esophagitis.¹⁰³⁻¹¹⁰ No data about vaccine efficacy and safety are available for patients treated with mepolizumab. Benralizumab is a humanized afucosylated anti-IL-5R α mAb, approved for severe eosinophilic asthma by the FDA in patients older than 12 years and by the EMA in adults. A recent randomized controlled trial demonstrated a good specific antibody response to quadrivalent influenza vaccine in adolescents and young adults with moderate-to-severe asthma treated with medium- to high-dose inhaled corticosteroid-long-acting beta 2 agonists and benralizumab.¹¹¹ No data on vaccine efficacy and safety are available for patients treated with reslizumab, a recombinant humanized IgG4 anti IL-5 monoclonal antibody currently approved by the FDA and the EMA in adults with severe refractory eosinophilic asthma.

VACCINATION AGAINST COVID-19

The COVID-19 pandemic was declared by the World Health Organization (WHO) on March 11, 2020. A huge scientific and economic effort has been made to develop safe and effective vaccines against severe adult respiratory syndrome coronavirus 2 (SARS-CoV-2). To date in Europe, 4 vaccines are in use after approval by the EMA: 2 mRNA vaccines (BNT162b2; mRNA-1273) and 2 viral vector vaccines using harmless adenoviruses (ChAdOx1-SARS-CoV-2, Ad26.COV2.S).¹¹² Vaccines currently available have not been initially tested in the vulnerable population, particularly in either patients with immune-mediated disorders or those on biologic drugs. These patients are assumed to be more susceptible to SARS-CoV-2 infection and severe COVID-19 owing to immune impairment; however, the impact

TABLE II. Recommendations for vaccination in patients receiving IMBs

Patients receiving IMBs have an increased risk of infectious diseases and associated complications with a significant burden of morbidity and mortality. To date, there is no well-established evidence for use of vaccines in these patients.
Vaccine schedule should be individualized according to the clinical and immunological status of the patient.
Patient's vaccination status should be documented and incomplete vaccinations should be completed whenever possible prior therapy.
Patients on IMBs should be advised of potential suboptimal immune response.
Inactivated vaccines should be preferably administered at least 2 wk before the initiation of biologics.
Live-attenuated vaccines are generally contraindicated during and for weeks to months following discontinuation of the IMB. They should be administered at least 4 wk before the initiation of therapy.
There is no need to routinely assess antibody titers either before or after the vaccination program because they may not be predictive of long-term protection because cellular immunity can persist regardless of antibody levels.

of COVID-19 and the safety and efficacy of currently available COVID-19 vaccines in these patients are still questioned. As knowledge grows, in accordance with interim indications for primary immunodeficiency patients,¹¹³ The COVID-19 vaccines should be administered according to their national vaccine schedule, unless contraindicated. Live vaccines, should they become available in the future, should follow the same contraindications for existing live vaccines.¹¹⁴ So far, these patients receiving COVID-19 vaccines should be advised on (1) limited data on vaccine safety and efficacy profiles in the immunocompromised, (2) the potential for a suboptimal immune response, and (3) the need to follow current preventive guidelines against COVID-19.

VACCINATION IN PREGNANCY AND BREAST FEEDING

Whether biologics administered during pregnancy and/or breast feeding affect child health and immunological development is still unknown. Because biologics are derivatives of IgG, they cross the placenta during the third trimester by existing transport pathways (eg, FcRn receptors), although with different relevance according to specific IgG subclasses, and achieve high serum levels in the child when administered after gestational week 30.¹⁸ According to EULAR experts' consensus, children exposed to IMBs before gestational week 22 can receive vaccinations, according to national protocols, including live vaccines. Prior to delivery, children exposed after that gestational age can follow vaccination schedules, but should not receive live vaccines up to the first 6 months of life.^{18,115}

VACCINATIONS FOR HOUSEHOLD MEMBERS AND CAREGIVERS

Close contacts of patients on IMBs should follow the same recommendations as for immunocompromised patients^{33,45,116} that are hereby summarized:

1. Inactivated vaccines are strongly recommended.
2. Measles, mumps, rubella, and rotavirus can be administered to susceptible family members or other close contacts because there is no evidence of human-to-human transmission of live-attenuated MMR vaccine. However, those vaccinated against rotavirus should avoid changing the diaper of children in the 4 weeks post immunization.
3. Vaccination against VZV is recommended to relatives with no personal history of infection. In adult contacts, it is also suggested to verify seroreactivity against VZV because they may not be protected by previous natural or passive immunization.
4. Inactivated influenza vaccine is recommended whereas live-attenuated vaccine is contraindicated.
5. Vaccination with live polio vaccine is contraindicated: only inactivated vaccine should be administered.

DISCUSSION

Biologics are growing in number and in their clinical use in several fields of medicine, and this is likely to continue (Table II). To date, there is no well-established evidence for use of vaccines in patients on biologic drugs, especially in the pediatric population in which most recommendations are transferred from the evidence and experience in adult patients. Patients on IMBs represent a very heterogeneous population with regard to degree of immunosuppression and susceptibility to infection. Moreover, vaccine immunogenicity can differ from the healthy owing to the disease itself or the immunosuppressive treatment. Although evidence on vaccine efficacy in terms of infection rate is lacking, vaccine safety issues in patients on most IMBs are encouraging owing to low serious adverse events or low risk to worsen the underlying disease activity. Safety concerns essentially regard live vaccines; however, multifactorial interactions may affect immunogenicity and efficacy to select vaccines. Indeed, vaccine schedule should be individualized according to the clinical and immunological status of the patient. Once IMBs have been planned, the patient's vaccination status should be documented and incomplete vaccinations should be completed whenever possible. If the treatment has already been started, vaccinations should be administered ideally during disease remission and when the immunosuppression is at its lowest level. Patients on IMBs should be advised of a potential suboptimal immune response. Inactivated vaccines should be preferably administered 2 weeks before the initiation of biologics. Conversely, live-attenuated vaccines are generally contraindicated during and for weeks to months following discontinuation of the IMB. Live vaccines should be administered at least 4 weeks before the initiation of biologic drugs, unless contraindicated by a condition or other therapies. Serology testing for VZV and HBV should also be considered. Low persistence of protective antibody levels has been demonstrated for some pathogens because the biologic therapy seems to accelerate the decline of vaccine-induced antibody concentrations. Therefore, in these cases, administration of booster vaccines is important to ensure long-term protection. In general, there is no need to routinely assess antibody titers either before or after the vaccination program, because they may not be predictive of long-term protection because cellular immunity can persist regardless of antibody levels. Specific antibody testing should be considered case by case. Studies on post vaccine cellular response in children on biologic agents are required to

evaluate its role in long-term protection against vaccine-preventable diseases and to design the optimal vaccine schedule.

Briefly, protection of children receiving biologics is a priority, and as new data emerge, the potential risk of vaccine adverse effects or suboptimal responses should be appropriately balanced. This document summarizes current literature data as well as the SIAIP Vaccine Committee and the IPINet real-life practice to provide a useful guidance for clinicians and a contribution to improve the health and care of these patients.

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