Vaccinations in children and adolescents treated with immune modifying biologicals: update and current developments

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Abstract

Treatment with immune modifying biologicals 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 biologicals, 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 biologicals. Our aim is to provide a practical guidance for the clinician to ensure optimal protection for patients and the community.

Introduction

Over the past two decades immune modifying biologicals (IMB) have revolutionized the treatment of immune-mediated and autoinflammatory diseases , due to their efficacy, fast action and good tolerability. IMB 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 IMB 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 towards 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 biologicals are needed due to current limited evidence.

In this paper we provide a practical approach to help the clinician in the vaccine decision process for children receiving biologicals 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.

Monoclonal antibodies and selective immune suppressors (Table 1)

B cell targeting agents

Rituximab and anti-CD20 mAbs family

Rituximab is an anti-CD20 monoclonal antibody that was first approved for the treatment of oncological disorders and further extended to several immunological diseases in adults and children. In recent years, many other anti-CD20 analogues (e.g. ofatumumab, ocrelizumab) have been developed. With B cell depleting anti-CD20 monoclonal antibody therapy, targeting from pre-B cells to plasmablasts, except pro-B cells and 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 not only affects 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 efficacy of inactivated vaccines is altered due 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]. B cell recovery after anti-CD20 mAbs therapy mostly occurs within 6-12 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 since vaccine responses have been reported to be blunted, although present, with B cell aplasia [9]. However, as an optimal humoral response is unlikely to be obtained during the B cell depletion phase, it is recommended to postpone inactivated vaccines for 6-12 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. As 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 erythematous (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 $CD19^+$, $CD20^+$, naïve, 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. As memory B cells are usually only partially affected, vaccine responses should not be impaired. In a small randomized study, antibody titres to previous pneumococcal, TT, and influenza immunizations were not affected in patients with SLE [15]. Non-live vaccines have been safely administered in patients on 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 titre [15]. A randomized clinical trial showed comparable proportions of responders to 23-valent pneumococcal polysaccharide vaccine 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]. Since no more data are available , inactivated vaccines are strongly encouraged in patients with SLE receiving IMB , including belimumab [18]. Conversely, due 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

CTLA-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 (CTLA4) and the constant region of IgG1, abatacept act as a blocker of cognate T cell-antigen presenting cell (APC) interactions, by binding CD80/CD86 on APC 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 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 two weeks after treatment with abatacept, whereas the patients who were vaccinated before treatment reached higher specific antibody titres than those who received vaccination after abatacept. However, immunological studies in patients with rheumatoid arthritis (RA), receiving a combination of diseases modifying anti-rheumatic drugs (DMARDs), reported variable effects of inactivated vaccines. Some authors reported blunted immunization response to seasonal influenza [6,23], while others observed protective titres for both influenza and PPV, as in healthy subjects [24,25]. Notably, opsonisation 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 on 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. As 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 monoclonal antibody 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 allogenic stem cell transplantation. As 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 one 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 PPV 23-valent, tetanus toxoid, 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]. It is recommended to screen patients ahead of planned infusion and offer anti-VZV vaccination at least 6 weeks before treatment starts[33,34].

Complement component blockers

Complement inhibitors have entered in clinical practice for treatment of haematological conditions triggered by an uncontrolled and/or exuberant complement activation (e.g. paroxysmal nocturnal haemoglobinuria, atypical haemolytic–uremic syndrome, complement-associated thrombotic microangiopathy) [35–37]. Eculizumab was the first humanized monoclonal antibody approved for treatment of transfusion-dependent paroxysmal nocturnal haemoglobinuria 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 (MAC). As only the terminal complement system is blocked, the proximal cascade, responsible for opsonisation of microorganisms and clearance of immune complexes, remains functional. However, as for patients with genetic dysfunction of C5 [38], blocking terminal complement activity and MAC formation increases patients' susceptibility to *Neisseria spp.* infections. Indeed, both clinical trials and case reports showed a notable 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 to plan immunization with a tetravalent meningococcal vaccine (MenACWY) 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 8/12 weeks are recommended. Booster doses should be given every 5 years in long-term, treated patients. Similarly, also anti-MenB vaccination, administered in two 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 titres [41]. Although the risk of other encapsulated bacteria infection is not as noticeable as for *Neisseria spp.*, anti-pneumococcal and anti-Hib vaccination are also recommended before starting eculizumab. The FDA recommends to keep 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]

TNFα Inhibitors

Tumor necrosis factor alpha (TNFα) is a proinflammatory 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 (IMIDs) such as juvenile idiopathic arthritis (JIA), psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis and plaque psoriasis. TNF agents are also used off-label to treat steroid-refractory graft-versus-host disease (GVHD) and other serious immune-mediated conditions (e.g. Kawasaki disease) [47]. The approved TNF-alpha blockers that differ in their structures, pharmacokinetics and mechanism of action are etanercept (a soluble p75 TNF-alpha receptor/IgG-Fc fusion protein), infliximab (a chimeric mouse/human anti-TNF-alpha antibody), adalimumab (a fully human monoclonal anti-TNF-alpha antibody), certolizumab pegol (an antigen-binding fragment (Fab') of a humanized monoclonal antibody coupled to polyethylene glycol) and golimumab (a human anti-TNF-alpha monoclonal antibody) [48].

Inactivated vaccines

According to EULAR (*European League Against Rheumatism*) recommendations, non-live vaccines can be administered to pediatric patients with rheumatic diseases using anti-TNFα 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 TNFα blockers treatment because serious adverse events or disease deterioration were not observed. Although several studies proved that TNFα inhibitors did not reduce specific antibody rates in those patients who were vaccinated during treatment, some authors found lower antibody production to PPV23 (pneumococcal polysaccharide vaccine), some serotypes of PCV7 (heptavalent pneumococcal conjugate vaccine), influenza, Meningococcal C and Hepatitis A vaccinations compared to healthy subjects or patients treated with treatments

other than TNFα blockers [49,50,54,55]. To ensure adequate immune responses, the EULAR task force advises to consider measuring post-vaccine antibody titers in patients on anti-TNFα therapy. Prior to starting TNFα 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. HBV seronegative patients should receive the vaccine cycle and recheck titers one 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 4-6) or an accelerated schedule (months 0, 1, and 2) [50]. According to a recent review, previously vaccinated adolescents with IBD, in which anti-HBs is not detectable, should receive a second 3-dose and/or a single high-concentration HBV vaccine (dose 40 mcg/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-TNFα 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 methotrexate (MTX) and anti-TNFα therapy (etanercept, infliximab, adalimumab and golimumab) for > 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-TNFα may also induce accelerated post- meningococcal C vaccine antibody waning, with the need of revaccination [54]. Due 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 al. showed a reduced immune response in children with juvenile idiopathic arthritis (JIA) treated with etanercept

compared to patients treated with conventional DMARDs and healthy controls [49,59,60]. 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 serologic protection. Thus, this suggests that influenza vaccine may be administered at any time during infliximab schedule [61]. According to a study on adult patients with rheumatoid arthritis and ankylosing spondylitis, administration of influenza vaccine on the same day of infliximab infusion seems to improve humoral response 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-TNFα agents in particular infliximab or adalimumab, 29 healthy controls) demonstrated safety and immunogenicity of booster pertussis vaccine, irrespective of treatment type [63]. According to local epidemiology, it is recommended to adhere to national vaccine guidelines also for vaccinations against cholera, Japanese encephalitis, rabies, tickborne encephalitis and typhoid fever, even though data are scarce, especially in patients treated with anti-TNFα.

Live-attenuated vaccines

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 one and three years after starting TNFα blockers. 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–TNFα treatment. Rubella and measles-specific-IgG concentrations were not affected by age, gender, high disease activity at diagnosis, time interval between the two MMR vaccine doses as well as time lapse from last MMR vaccination to beginning of adalimumab [64]. The aforementioned Swedish study

found that children with rheumatic diseases treated with MTX and anti-TNFα for at least 3 months, who have only received one dose of MMR vaccine, had lower levels of measles-specific memory B cells compared to healthy controls. Conversely, specific memory B cells (MBC) 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 (YFV) booster vaccine was observed in patients on TNFα blocking agents, although reduced responses were registered [49,65]. Long-term safety of varicella vaccine was reported in six children with JIA treated with biologics (3 etanercept, 2 tocilizumab, 1 infliximab) , although adequate protection against varicella infection was not always provided since one patient got mild varicella 4 months after the second vaccine dose [66]. Another study confirmed safety of varicella vaccine [67]. In a cohort of 23 pediatric rheumatic disease patients receiving immunosuppressive therapy (i.e., adalimumab, etanercept and infliximab), who were at risk for serious chickenpox, the monovalent varicella zoster virus (VZV) vaccine was well-tolerated and immunogenic [68]. Serious VZV infections are the major concerns especially in immunocompromised patients receiving TNFα inhibitors, therefore these patients should be screened for this virus before commencement of these biologicals and varicella vaccination should be individually considered based on local epidemiology for the risk of varicella exposure [33,49,51].

Lee AM et al. investigated 38 acute Kawasaki disease (KD) patients, aged < 18 months or 4-6 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-TNFα agents showed no BCG-related severe adverse events, including disseminated BCG 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-TNFα agents may reduce vaccine responses compared to 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]. Additionally, antibody levels seem to decline more rapidly over time in patients using anti-TNFα 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 (IL-6) inhibitors

Interleukin-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 defence mechanisms against pathogens. Anti- IL-6 family inhibitors, including anti-IL-6R alpha chain (IL-6Rα) and anti-IL6 itself, represent one of the accepted treatments for several autoimmune and inflammatory conditions including rheumatoid arthritis (RA), Castleman's disease, and giant cell arteritis [72]. Tocilizumab (TCZ) is a humanized anti-interleukin6 receptor (IL-6R) monoclonal antibody accepted for several diseases such as rheumatoid arthritis (RA), Castleman's disease, polyarticular and systemic juvenile idiopathic arthritis, 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 sclerosis [74], and in 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 23 valent pneumococcal vaccines (PPV23) in 28 RA patients treated with TCZ has been reported [76]. Two larger studies demonstrated the efficacy of flu and PPV23 vaccines in two 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 observed after MTX therapy with other biological drugs [81–84]. Of note, response to pneumococcal conjugate heptavalent vaccine (PCV7) was not affected during TCZ treatment, unlike what occurs during rituximab (anti CD20) and abatacept (CTLA-4 pathway modifier) therapies [6]. Moreover, the influenza vaccine demonstrated a comparable efficacy to healthy controls in a cohort of 27 patients with systemic-onset JIA treated with TCZ, regardless of treatment duration [79]. Lastly, a randomized controlled trial showed a non-significant reduction of response to PPV23 and tetanus toxoid 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, due 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-6Rα) and siltuximab (anti-soluble and membrane-bound IL-6Rα).

IL-17 axis

Interleukin 17 (IL-17) inhibitors

IL-17 cytokine is involved in the immune response and clearance of both extracellular and intracellular pathogens [86]. IL-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 G-CSF [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 psoriatic arthritis [87]. Secukinumab is a human anti IL-17A monoclonal antibody approved for the treatment of plaque psoriasis, psoriatic arthritis (PsA), ankylosing spondylitis and non-radiographic axial spondylarthritis (nrAxSpA) [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, where 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 vaccines [90]. Ixekizumab (IXE) is a humanized anti-IL-17A monoclonal antibody 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. 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 to the control group, and the vaccines were well tolerated [91]. No severe adverse events nor disease relapse have 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 ixekizumab 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 12-23 (IL-12-23) inhibitors

Interleukin-23 cytokine, produced by antigen-presenting Langerhans cells, dendritic cells and monocytes/macrophages due to inflammatory or biochemical damage of barrier sites (i.e., skin, gut and entheses), increases number and activity of Th17 cells, enhancing IL-17 production [92]. Blocking IL23 signalling allows a downregulation of Th17 cell function with a decrease of circulating IL17A [92]. Ustekinumab is a human anti IL12-23 monoclonal antibody approved for the treatment of plaque psoriasis (both in adults and children), psoriatic arthritis, Crohn disease (CD) and ulcerative colitis (UC). Ustekinumab is responsible for the downregulation of both Th1 and Th17 cells development as well as T follicular helper (TFH) cell generation. TFH 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 CD adult patients treated with ustekinumab vs 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 pneumococcal vaccine [96]. Also, a higher antibody response to hepatitis B vaccine in patients treated with ustekinumab vs 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 IL23 monoclonal antibody approved for the adult treatment of moderate-to-severe plaque psoriasis.

Interleukin 1 (IL-1) inhibitors

IL-1a and IL-1b represent the major components of the interleukin-1 (IL-1) family and play a key role in the inflammatory response, with strong proinflammatory actions. Both IL-1a and IL-1b bind IL1-R and IL-1RAcP, activate nuclear factor-kB (NFKB) transcription with consequent neutrophil recruitment and pro-inflammatory mediator production. Anakinra is a IL1 recombinant non-glycosylated receptor antagonist targeting Interleukin 1 receptor I (IL1RI) which impairs both IL-1a and IL-1b functions. It is approved for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) and Rheumatoid Arthritis (RA) [99]. Canakinumab is a Human anti IL-1b monoclonal antibody approved in patients > 2 years of age by the European Medicine Agency for the treatment of CAPS TNFR-associated periodic syndrome, hyper-IgD syndrome/mevalonate kinase deficiency, familial Mediterranean fever as well as for adult-onset Still's disease and refractory systemic juvenile idiopathic arthritis [43]. Data on vaccine efficacy and safety during treatment with IL1-inhibitors are extremely poor. No difference in antibody response to tetanus 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 sub-cutaneous canakinumab, no impairment of antibody responses to non-adjuvanted influenza and serogroup C meningococcal conjugate vaccines and no severe adverse events were reported [100]. Live-attenuated vaccines are not be recommended for lack of data.

Interleukin 4 (IL-4)/ Interleukin 13 (IL-13) inhibitor

IL-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 STAT6 signalling pathway which enhances allergic inflammation [101]. Dupilumab is a human IgG4 anti-IL4 receptor α (IL-4Rα) monoclonal antibody acting through the inhibition of both IL-4 and IL-13 signalling. Dupilumab has recently been approved in patients ≥ 6 years of age 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]. Due to the lack of safety and efficacy data, live-attenuated vaccines should be avoided during dupilumab treatment.

Interleukin 5 (IL-5) inhibitors

IL-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 monoclonal antibody, approved by FDA and EMA as an add-on therapy for severe refractory eosinophilic asthma and by FDA in adults with chronic rhinosinusitis with nasal polyps (CRSwNP). 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 hyper-eosinophilic 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-5Rα monoclonal antibody, approved for severe eosinophilic asthma by FDA in patients > 12 years of age and by 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 ICS-LABA 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 FDA and EMA in adults with severe refractory eosinophilic asthma.

Vaccination against COVID-19

Since COVID-19 pandemic was declared by WHO on 11 March 2020 a huge scientific and economic effort has been made to develop safe and effective vaccines against SARS CoV-2 To date in Europe, four vaccines are in use after approval by the European Medicine Agency: two mRNA vaccines (BNT162b2; mRNA-1273) and two 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 either in patients with immune-mediated disorders or on biological drugs. These patients are assumed to be more susceptible to SARS-CoV-2 infection and severe COVID-19 due to immune impairment, however the impact of COVID-19 and 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], COVID-19 vaccines should be advised 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. (*https://esid.org/COVID-19/ESID-COVID-19-Statement*). 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 3) the need to follow current preventive guidelines against COVID-19.

Vaccination in Pregnancy and Breast feeding

Whether biologicals administered during pregnancy and/or breast feeding affect child health and immunological development is still unknown. Since biologicals are derivates of IgG, they cross the placenta during the third trimester by existing transport pathways (e.g.

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 IMB 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 [18,114].

Vaccinations for household members and caregivers

Close contacts of patients on IMB should follow the same recommendations as for immunocompromised patients [33,45,115], that are hereby summarized:

a) Inactivated vaccines are strongly recommended.
b) Measles, mumps, rubella and rotavirus can be administered to susceptible family members or other close contacts since 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.
c) Vaccination against varicella/zoster virus is recommended to relatives with no personal history of infection. In adult contacts, it is also suggested to verify seroreactivity against varicella since they may not be protected by previous natural or passive immunization.
d) Inactivated influenza vaccine is recommended whereas live attenuated vaccine is contraindicated.
e) Vaccination with live polio vaccine is contraindicated: only inactivated vaccine should be administered.

Discussion and conclusion

Biologicals are growing in number and in their clinical use in several fields of medicine, and this is likely to continue. To date there is no well- established evidence for use of vaccines in patients on biological drugs, especially in pediatric population where most recommendations are transferred from the evidence and experience in adult patients.

Patients on IMB represent a very heterogeneous population with regard to degree of immunosuppression and susceptibility to infection. Moreover, vaccine immunogenicity can differ from the healthy, due 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 IMB are encouraging due 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 IMB have been planned, 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 IMB should be advised of potential suboptimal immune response. Inactivated vaccines, should be preferably administered 2 weeks before the initiation of biologicals. 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 since the biological 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, since they may not be predictive of long-term protection as cellular immunity can persist regardless of antibody levels. Specific antibody testing should be considered case by case. Studies on postvaccine cellular response in children on biological agents are required to evaluate its role in long-term protection against vaccine-preventable diseases and design optimal vaccine schedule. Briefly, protection of children receiving biologicals 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

Italian Society of Pediatric Allergy and Immunology (SIAIP) Vaccine Committee and the Italian Primary Immunodeficiency Network (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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