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Vaccination in Patients with Rheumatoid Arthritis Receiving Immunotherapies

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Abstract

Patients with rheumatoid arthritis (RA) are at higher risk to suffer from morbidity due to vaccine-preventable diseases and, thus, display an important target population to receive vaccines for protection from infectious complications. There have been only a few studies focusing on the administration of vaccines in RA patients with immunotherapy. Overall, antibody response rates against influenza or pneumococcal disease appeared to be only slightly lower than expected in healthy individuals.

Crucial problems in the interpretation of data from studies in RA patients vaccinated against influenza and pneumococcal disease are the impaired comparability of studies due to different study designs and type of vaccines used, different health states among RA patients, heterogeneity in treatments including concomitant therapy with conventional DMARDs and glucocorticoids in addition to biological agents.

Assessment of vaccination status should be performed in the initial work-up of patients with RA and should ideally be administered before initiation of immunotherapies or during stable disease. Due to differences in antibody responses and uncertainty regarding maintenance of protective antibodies, routine controls for antibody titers and specific strategies for earlier re-vaccination might be scheduled for patients with RA.

Keywords: Immunotherapy; Anti-TNF-alpha agents; Rituximab; Tocilizumab; Abatacept; Pneumococcal vaccination; Influenza vaccination

Introduction

Patients with rheumatoid arthritis (RA) are at high risk of developing infections, which may be due to the immunomodulatory effect of the disease itself and to the immunosuppressive effects of glucocorticoids, disease-modifying anti-rheumatic drugs (DMARDs) (e.g. methotrexate) and immunotherapies with biologic drugs, such as therapy targeted against tumor-necrosis-factor-alpha (TNF-α) and interleukin-6 (IL-6) or against B cells using anti-CD20 antibodies [1-5]. The use of glucocorticoids, concomitant DMARD treatment during anti-TNF-α therapy, advanced age at the start of anti-TNF-α therapy and the use of infliximab or adalimumab rather than etanercept were strong predictors of infection [5].

Influenza and pneumococcoal infections are two vaccine-preventable infectious diseases which have been associated with high morbidity in patients with RA [2,6,7] due to the autoimmune disease itself [8] or immunosuppressive treatments [9,10]. The awareness of the possibility to prevent influenza infections and invasive pneumococcal disease by vaccination and the number of effectively performed vaccinations vary within the group of RA patients [6,11].

In view of these data highlighting the increased risk of infectious diseases in RA patients receiving immunomodulatory or immunosuppressive treatments on the one hand and differences in awareness and performance of vaccinations, e.g. against influenza or pneumococcal infections, on the other hand, the need for clear recommendations for vaccinations under use of biologic agents is demanding. However, data on immunogenicity, efficacy and safety of vaccinations in RA patients on immunotherapy are rare and difficult to compare due to heterogeneity in the disease course itself, in treatments, study designs and type of vaccines [12]. Thus, the review elucidates the aspects of immunogenicity, efficacy and safety with special focus on influenza and pneumococcal vaccination in RA patients treated with biologic agents following a systematic review of literature.

Methods

Primary information from published data in PubMed between January 1990 and December 2012 were considered for systematic review by using the search terms “abatacept”, “adalimumab”, “anakinra”, “certolizumab”, “etanercept”, “golimumab”, “infliximab”, “rituximab” or “tocilizumab” combined with Medical Subject Headings (MeSH terms) “rheumatoid arthritis” and “vaccination” limited to publications in English, to human studies and original studies. The recommendations of “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) statement was applied to identify articles, to screen the abstracts for exclusion criteria (non-human studies, reviews, case reports, reports on secondary data) and to assess eligibility of full-text articles for inclusion of articles into qualitative data analysis and narrative reporting [13]. Reviews and reports on secondary data were excluded from evaluation, but cited in some cases when appropriate to provide additional literature on the topic. Case reports were used for illustration of single case experiences. Experiences with vaccinations in other autoimmune disorders (e. g. juvenile idiopathic arthritis, ankylosing arthritis, psoriatic arthritis) treated with immunotherapies were reported when being of interest for comparison with reports on RA or in cases of missing data for RA patients.

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Research for abatacept revealed 8 articles, of them 2 articles were included into review, research for adalimumab 11 articles (including 5), for etanercept 17 (including 7), for infliximab 22 (including 9), for rituximab 15 (including 6) and for tocilizumab 1 article (included). No articles were found for anakinra, certolizumab and golimumab.

Results

Influenza and Pneumococcal vaccinations

Anti-TNF-α agents: TNF enhances antibody function and promotes B cell proliferation [14]. In view of these facts, it is of concern whether antibody responses may be impaired by anti-TNF-α agents, such as etanercept, adalimumab and infliximab, used in the treatment of RA.

Etanercept is a soluble TNF receptor that inactivates the function of TNF. Infliximab is a chimeric monoclonal antibody directed against TNF. Adalimumab is a human, monoclonal antibody against TNF and neutralizes the effects of TNF by inhibiting its interaction with TNF-RI/II cell-surface receptors [15].

Influenza vaccination: Several studies on vaccination against influenza infection in RA patients considered anti-TNF-α agents, although the three approved anti-TNF-α drugs were not separately assessed in most studies.

Some results exist from RA patients treated with adalimumab or placebo from approval studies. In a double-blind, randomized, multicenter study, patients received adalimumab or placebo on days 1, 15 and 29 and were vaccinated with 23-valent pneumococcal and influenza vaccines on day 8 [16] (Table 1). Vaccine responses to pneumococcal antigens were similar in the adalimumab and the placebo group, as well as percentages of individuals with protective antibody titers [16]. Percentages of adalimumab treated patients achieving a vaccine response to influenza were generally lower than found in the placebo group [16]. This result was explained by the subgroup of patients with pre-existing protective antibody titers at baseline. For RA patients without protective antibody titers at baseline the percentages of responding adalimumab-treated patients and patients with protective antibody titers after vaccination were similar to the placebo group [16].

Some results exist also for infliximab compared to other treatments than anti-TNF-α agents. In a study comparing 20 RA patients with a mean dose of 3 mg/kg infliximab and 23 RA patients on DMARDs other than anti-TNF-α agents and 17 healthy controls, split-virion inactivated influenza vaccine (containing influenza A/H3N2, A/H1N1 and influenza B) was administered on the day of administration of infliximab or 3 weeks after infliximab [17] (Table 1). In RA patients receiving the vaccine 3 weeks after administration of infliximab the increase of geometric mean titers (GMTs) was not significant for H1N1 and H3N2. The percentage of responders were similar in all groups with no influence of age, gender, methotrexate or glucocorticoid use [17]. The disease activity remained unchanged in vaccinated patients [17]. In that study it was expected that the effect of infliximab would be maximal with the concomitant administration of the vaccine, however, the timing seemed not to influence the response to the influenza vaccine [17].

However, most studies did not distinguish between the different anti-TNF-α drugs approved for treatment of RA. In the past three years, many studies originated from the urgent demand to vaccinate RA patients during pandemic influenza.

In a study including 41 RA patients with all three anti-TNF-α agents and 41 RA patients on DMARDs alone, similar seroconversion rates were reported after non-adjuvanted, inactivated split-virion pandemic influenza A H1N1 vaccination compared to 117 healthy controls with a negative effect of methotrexate on the vaccine-specific response [18] (Table 1). Evaluating the immunogenicity of inactivated non-adjuvanted pandemic H1N1 vaccine among 258 RA patients with an unreported number of patients on anti-TNF-α therapy the proportions of seroprotection, seroconversion and GMT ratios post-vaccination were similar to elderly persons ≥60 years of age [19] (Table 1). Another study also presented data that anti-TNF-α agents did not severely diminish seroprotection rates [20] (Table 1). In addition, glucocorticoids did not seem to influence the immunogenicity of pandemic MF59-adjuvanted H1N1influenza vaccination in RA patients [20].

However, some other studies could not confirm the similar response to influenza vaccination in RA patients treated with anti-TNF-α agents compared to RA patients on DMARDs alone or to healthy individuals. In a study including 343 RA patients with an unreported number of anti-TNF-α treatment and a small proportion of rituximab use (0.8% in the whole group of 1668 patients with autoimmune rheumatic disease), a lower seroprotection rate against non-adjuvanted influenza A/H1N1 vaccine was reported compared to 234 healthy controls after immunization [21] (Table 1). Regardless of anti-TNF-α therapy (n=47) or not (n=293), lower GMTs, factor increase in GMTs and postvaccination seroprotection rates were found after adjuvant-free pandemic influenza A/H1N1 vaccination [22] (Table 1). However, methotrexate was the only DMARD associated with the reduced response [22]. Unlike to the other reported studies [18-20], disease activity did not influence the vaccine-specific responses [22].

Immunization against seasonal influenza infection is generally recommended in RA patients [23,24]. Vaccination with trivalent influenza vaccine (A/H1N1, A/H3N2, B) was performed in 50 RA patients treated with anti-TNF-α agents (etanercept or infliximab) in combination with methotrexate, 62 RA patients receiving anti-TNF-α agents alone or with other DMARDs than methotrexate and 37 RA patients treated only with methotrexate and 18 healthy controls [25] (Table 1). In that study, post-vaccination GMT increased significantly compared to pre-vaccination titers in all treatment groups and controls and also to each strain and percentages of responders were similar. The serological response was better in RA patients treated with methotrexate alone [25].

In another study, the percentage of responders to inactivated influenza vaccine was generally lower in 82 RA patients treated with various DMARDs (infliximab in 22 cases, etanercept in 5 cases) compared to 30 healthy controls, but was not affected by prednisone treatment or any DMARD, including methotrexate, infliximab and etanercept [26] (Table 1).

A study including a mixed group of 112 patients with different autoimmune diseases, containing 79 RA patients, demonstrated lower postvaccination GMTs against influenza antigens (A/H3N2 and B) in patients treated with anti-TNF-α agents compared to patients not on anti-TNF-α agents and healthy controls (n=18) [27] (Table 1). However, protection rates were not lower in the anti-TNF-α treated group [27].

A favorable outcome with protective antibody responses against influenza antigens at least 6 months after vaccination with non-adjuvanted influenza vaccine over three consecutive influenza seasons

Ref.	Study* design	Population	n	anti-TNF-α therapy (n)	Patients on methotrexate (%)	Vaccines	Effect in RA patients	Lower response[i]
[16]	P, DB, R, PC, MC	RA RA	99 109	a (99) ---	56.0 54.0	PPV and TIV	PPV: Vaccine responses[a] in adalimumab (37.4%) and placebo group (40.4%) and percentages of individuals with protective antibody titers[b] (adalimumab: 85.9%; placebo: 81.7%) similar TIV: Percentages of responding RA patients on adalimumab (51.5%) lower than in the placebo group (63.3%) RA patients without protective antibody titers at baseline: percentages of responding adalimumab-treated patients (73.3%) similar to the placebo group (73.9%), as well as percentages of individuals with protective antibody titers after vaccination (adalimumab: 98%; placebo: 94.5%)	No Yes No No
[17]	C, SC	RA AS HC	43 18 17	i (20) i (18) ---	81.3 66.7 ---	TIV	RA patients vaccinated 3 weeks after administration of infliximab: increase of geometric mean titers (GMTs) was not significant for H1N1 and H3N2 Percentage of responders[c] similar in all groups	Yes No
[18]	P, C, SC	Anti-TNF-α (n=120): RA AS PsA DMARDs alone (n=116): RA AS PsA HC	 41 57 22 41 75 53 117	e (26) a+i (94) --- --- --- ---	35.8 53.4	pIV	Similar seroconversion rates[d] compared to 117 healthy controls Negative effect of methotrexate on the vaccine-specific response	No
[19]	P, MC	RA JIA HIV Cancer KTX Elderly	258 83 255 319 85 149	n. r.	n. r.	pIV	Proportions of seroprotection, seroconversiond and GMT ratios post-vaccination were 61.5%, 53.1% and 7.5 similar to elderly persons ≥ 60 years of age (63.1%, 55.7% and 5.7)	No
[20]	C, SC	RA PsA AS SLE HC	41 17 15 21 25	a/e/i (3/5/5) (4/4/6) (2/2/8) --- ---	61.0 41.2 6.7 14.3 ---	pIV	Significant increase of GMTs in RA patients (5.7 to 64.3) (HC: 4.3 to 127) Proportion of respondersc significantly lower in RA patients (56%) compared to HC (84%) Seroprotection ratesd slightly lower in RA patients (71%) compared to HC (92%)	No Yes Yes
[21]	P, C, SC	RA ORD HC	343 1325 234	n. r. n. r. ---	n. r. n. r. ---	pIV	Factor increase of GMT in RA patients (7.2) lower than in HC (13.2) Seroconversion rate[d] in RA patients (53.4%) lower than in HC (76.9%) Seroprotection rate[d] in RA patients (60.1%) lower than in HC (82.9%)	Yes Yes Yes
[22]	P, C, SC	RA HC	340 234	a/e/i (16/11/20) ---	63.2 ---	pIV	Lower GMTs (71.9), factor increase in GMTs (9.6) and post-vaccination seroprotection rates[d] (67.4%) in RA versus HC (122.9, 13.2 and 82.9%, respectively)	Yes
[25]	C, SC	RA HC	149 18	n. c. (112) ---	58.4 ---	TIV	Postvaccination GMT increased significantly compared to pre-vaccination titers in all treatment groups and controls	No
[26]	C, SC	RA HC	82 30	i/e (22/5) ---	68.3 ---	TIV	Similar GMTs in RA compared to HC for all influenza antigens Percentage of responders to B antigen lower in RA (67%) than in HC (87%)	No Yes
[27]	C, SC	RA ORD	79 33	RA+ORD: a/e/i (21/14/29)	RA+ORD: 71.0	TIV	Lower postvaccination GMTs by anti-TNF-α treatment, without lowering protection rates	Yes No
[28]	C, SC	RA HC	28 10	n. c. ---	n. r. ---	TIV	Similar response in seroconversion and seroprotection rates[d] and in seroconversion factore	No
[30]	R, PC, MC	RA	70	i (56)	71.4	PPV	Although 80% to 85% of patients in the treatment groups responded[f] to at least one serotype, only 20% to 25% responded to ≥ 6 different serotypes	Yes
[31]	C, SC	RA HC	149 47	e/i (48/64) ---	58.4 ---	PPV	Immunization responseg was similar between RA and HC against serotype 23F and 6B	No
[32]	SC	RA	31	e/i (12/4)	65.0	PPV	Significant increase of GMTs to all 7 serotypes tested Lower proportions of RA patients on anti-TNF-α therapy with a >2-fold increase (e. g. 23F: 13% versus 53% not treated with anti-TNF-α)	No Yes
[34]	MC	RA SpA	253 252	n. c. (168)	RA+SpA: 68.8	PCV	Antibody response ratio[h] was higher in RA patients receiving anti-TNF-α alone (36.7%) compared to RA patients with methotrexate alone (21.2%) and anti-TNF-α and methotrexate (15.7%)	No
[35]	C, MC	RA† RA HC	253† 149 47	n. c.† (168) n. c. (112) ---	68.8† 58.4 ---	PCV† and PPV	Positive antibody response ratios and the positive antibody responseh were similar between the groups for the tested serotypes 23F and 6B	No

[a]A response to the vaccine was defined by a ≥ 2-fold titer increase from baseline at day 8 in ≥ 3 of 5 pneumococcal antigens and ≥ 4-fold increase from baseline in ≥ 2 of 3 influenza antigens [16]
[b]Protective antibody titers were defined by pneumococcal antibody concentrations ≥ 1.6 µg/ml to ≥ 3 of 5 antigens and by influenza antibody titers ≥ 1:40 to ≥ 2 of 3 antigens at 4 weeks after vaccination [16]
[c]A response to the vaccine was defined by a ≥ 4-fold rise in hemagglutination inhibition (HI) antibodies 4 to 6 weeks after vaccination or seroconversion in patients with a non-protective baseline level of antibodies <1:40 [17]
[d]Seroprotection was defined by influenza antibody titers ≥1:40 and seroconversion by pre-vaccination titer <1:10 and a post-vaccination HI titer ≥ 1:40 or a pre-vaccination titer ≥ 1:10 and a ≥ 4-fold increase postvaccination [18]
[e]The seroconversion factor was calculated by the post-vaccination antibody titer divided by the pre-vaccination antibody titer and was considered as cut-off level of vaccine immunogenicity for adults 18-60 years when exceeding 2.5 (2.0 in people aged >60 years) [28]
[f]A response was defined if postvaccination antibody levels met the threshold value used by Quest Diagnostics (Van Nuys, CA) or if there was a ≥ 2-fold increase in pre- to postvaccination antibody levels in ≥ 6 of the 12 serotypes [30]
[g]The immunization response was calculated as ratio of post- and prevaccination concentrations [31]
[h]A positive antibody response was defined as the antibody response ratio (ratio of post- to prevaccination antibody levels) of ≥ 2 [34,35]
[i]Response of RA patients compared to the comparator in the study
†Identical with [34]
*Study design is given as described in the corresponding reference

Abbreviations
Ref: Reference; P: Prospective Study; DB: Double-Blind Study; C: Controlled Study; PC: Placebo-Controlled Study; R: Randomized Study; SC: Single-Center Study; MC: Multi-Center STUDy; RA: Rheumatoid Arthritis; SpA: Spondylopathic Arthritis; AS: Ankylosing Arthritis; PsA: Psoriatic Arthritis; HC: Healthy Controls; KTX: Kidney Transplantation; JIA: Juvenile Idiopathic Arthritis; HIV: Human Immunodeficiency Virus; SLE: Systemic Lupus Erythematosus; ORD: Other Rheumatic Diseases; n. r.: not reported; n. c.: not classified for different anti-TNF-α agents; DMARDs: Disease-Modifying Anti-Rheumatic Drugs; a: adalimumab; e: etanercept; i: infliximab; PPV: 23-valent Pneumococcal Polysaccharide Vaccine; PCV: 7-valent Pneumococcal Conjugated Vaccine; TIV: Trivalent Influenza Vaccine; pIV: pandemic H1N1 influenza vaccine; GMT: Geometric Mean Titer

Table 1: Effect of anti-TNF-α therapy in rheumatoid arthritis patients on antibody responses to vaccinations.

was also reported in a study with 28 patients with low to moderate, stable RA on anti-TNF-α agents and confirmed vaccine safety [28] (Table 1).

However, some experience from patients with inflammatory bowel disease who were vaccinated against influenza revealed a higher risk of an inadequate response to vaccination in those treated with infliximab and concomitant immunomodulatory therapy with glucocorticoids, 6-mercaptopurine or methotrexate [29].

Overall, there is no consistent evidence of lower ability in mounting protective immune responses following influenza vaccination while being treated with anti-TNF-α therapy. Interestingly, according to the presented studies, different responses to the pandemic influenza vaccine compared to seasonal influenza vaccines were seen with no clear advantage of different vaccine preparations or adjuvanted formulations.

Pneumococcal vaccination: Pneumococcal vaccination is strongly recommended in patients with chronic diseases and immunsuppressive treatments to prevent from invasive pneumococcal disease [23]. Studies exist on the immune response to antigens contained in the 23-valent polysaccharide vaccine and in the conjugated pneumococcal vaccine.

Twenty RA patients who received infliximab 3 mg/kg plus methotrexate in the ASPIRE substudy, 36 RA patients who received infliximab 6 mg/kg plus methotrexate and 14 on placebo plus methotrexate were enrolled into a vaccination program administering 23-valent polysaccharide pneumococcal vaccine at 34 weeks after initiation of infliximab [30] (Table 1). The antibody responses were assessed 4 weeks after vaccination using an enzyme immunoassay for reactivity to a panel of the 12 serotypes of the pneumococcal vaccine [30]. RA patients under 45 years of age and those on oral glucocorticoids generally appeared to respond better than those aged 45 to 65 years and without oral glucocorticoids [30].

In a study analyzing 62 RA patients on anti-TNF-α therapy (infliximab: 27; etanercept: 35) alone, 50 RA patients on anti-TNF-α therapy (infliximab: 37; etanercept: 13) with methotrexate, 37 RA patients with methotrexate alone and 47 healthy controls, a significant increase of antibody concentrations against serotypes 23F and 6B after 23-valent pneumococcal vaccination was found in all groups [31] (Table 1). The highest response was found in RA patients treated with anti-TNF-α therapy without methotrexate, compared to those with concomitant methotrexate or methotrexate alone [31].

Comparing 16 RA patients on anti-TNF-α agents and 17 patients without anti-TNF-α agents, both groups had a significant increase of GMTs to all 7 serotypes tested after 23-valent polysaccharide pneumococcal vaccine [32] (Table 1). However, lower proportions of RA patients on anti-TNF-α therapy responded with a >2-fold increase [32].

Conjugate pneumococcal vaccines were supposed to induce a significant better T cell dependent response, particularly in children. Conjugate pneumococcal vaccination was successfully applied in children with juvenile idiopathic arthritis (JIA), but with less response against serotypes 4, 14 and 23F in those receiving anti-TNF-α agents [33] (Table 1). A ≥ 4-fold increase of baseline titers to ≥ 5 vaccine serotypes was found in 50% of JIA patients with anti-TNF-α agents plus DMARDs compared to 70% of JIA patients with DMARDs alone [33].

The use of conjugate pneumococcal vaccination was also investigated in adults with RA [34] and tested against plain polysaccharide vaccine [35] (Table 1). In study vaccinating 253 RA patients with different treatment regimens (85 receiving methotrexate alone, 89 anti-TNF-α agents and methotrexate and 79 anti-TNF-α agents alone), a better antibody response ratio to a single dose of 7-valent conjugate pneumococcal vaccine was seen in RA patients without methotrexate treatment [34]. In that study, methotrexate was thought to negatively influence the T cell dependent response to conjugate vaccines [34]. Using a logistic regression model, higher age at vaccination and concomitant methotrexate were identified as predictors of an impaired positive antibody response for both serotypes, whereas the type of vaccine has no influence on these parameters [34]. Those RA patients vaccinated with the 7-valent conjugate vaccine [34] were compared to 149 RA patients considering different treatment groups (methotrexate alone, anti-TNF-α agents and methotrexate and anti-TNF-α agents alone) and 47 healthy controls, both groups receiving a single dose of 23-valent polysaccharide vaccine [35]. Positive antibody response ratios and a positive antibody response were found to be similar between the groups for the tested serotypes 23F and 6B 4 to 6 weeks

after vaccination in all groups regardless of the type of vaccination [35].

Some experience also exists for inflammatory bowel disease with infliximab and 23-valent pneumococcal vaccination, demonstrating a significantly lower response rate in patients administered infliximab or combination immunsuppressive therapy (e.g. azathioprine) compared to the group only on mesalamine [36].

Abatacept

Abatacept, a CTLA4-immunoglobuline-fusion protein, inhibits T cell activation by binding to CD80 and CD86, thus, blocking the interaction with CD28. This effect results in modulation of the CD80/CD86:CD28 co-stimulatory signal which is required for full T cell activation. It has been approved for the treatment of RA in combination with methotrexate in a number of countries including the United States, Canada and the European Union.

In 1,955 patients treated with abatacept during the double-blind periods of the approval studies, and 2,688 during the cumulative double-blind and open-label periods, also aspects of immunogenicity, safety and efficacy of vaccines were studied showed a not markedly impaired response to tetanus toxoid and 23-valent pneumococcal vaccinations in healthy volunteers [37] and RA patients [38,39]. Antibody titers against non-adjuvanted monovalent pandemic 2009 influenza A/H1N1 vaccine were evaluated by hemagglutination inhibition (HI) assay in 11 RA patients treated with abatacept and concomitant non-biologic DMARDs compared to 33 age-matched RA patients on methotrexate and 55 healthy controls 21 days after vaccination [40]. Seroprotection (antibody titers ≥ 1:40) was significantly reduced in the abatacept-treated RA patients (9%) compared to RA patients on methotrexate (58%) and healthy controls (69%) [40]. The factor increase in GMTs was lower in abatacept-treated RA patients (1.8) compared to the methotrexate-treated RA patients (8.7) and healthy controls (11.5) [40].

Rituximab

Rituximab is a monoclonal antibody against CD20, which diminishes the number of circulating B cells for a period of 6 to 9 months after administration but does not affect circulating plasma cells or immunoglobulin levels. It is approved by American and European authorities for the treatment of RA patients in whom anti-TNF-α therapy failed [41].

The reports on the humoral immune response to influenza vaccination in RA patients treated with rituximab are conflicting. Significantly lower HI titers after trivalent influenza vaccination (influenza A/H3N2, A/H1N1 and influenza B) were observed in 4 RA patients on rituximab with a median B cell count $<10\times10^6$ cells/l compared to 19 RA patients on etanercept with or without DMARDs and 20 healthy controls [41].

In a study comparing 14 rituximab-treated RA patients, 29 RA patients treated with other DMARDs and 21 healthy controls vaccinated with a split-virion inactivated influenza A/H3N2 (California), A/H1N1 (New Caledonia) and influenza B (Shanghai) vaccine, a lower proportion of responders to the California antigen was found in the rituximab-treated group (21% responders versus 67% in the non-rituximab groups) [42]. In that study, a sufficient immune response was defined by an at least fourfold rise in HI titers 4 weeks after vaccination in patients with baseline titers ≥ 1:40 or a rise of HI titers ≥ 1:40 in patients with non-protective pre-vaccination titers <1:40. A response to more than one antigen was found in 14% of rituximab-treated RA patients, but in 48% of the non-rituximab patients and 40% of healthy controls [42]. The authors found no correlation between influenza vaccination and activity parameters, such as swollen and tender joint counts, duration of morning stiffness, level of pain, erythrocyte sedimentation rate or C-reactive protein levels, the use of glucocorticoids or methotrexate or frequency of $CD19^+$ B cells or time interval since receiving rituximab [42]. Higher proportions of responders to the California antigen were seen in patients treated with lower numbers of various DMARDs [42].

In another study, trivalent influenza vaccine (influenza A/H3N2, A/H1N1 and influenza B) was administered to 11 RA patients 4 to 8 weeks after rituximab (early rituximab subgroup) and to 12 RA patients 6 to 10 months after rituximab (late rituximab subgroup), which were compared to 20 RA patients receiving methotrexate and 29 healthy controls [43]. No increase of antibody titers against any vaccinated influenza strain was found in the early rituximab subgroup. Some recovery of the humoral immune response was seen in the late rituximab subgroup, with a significant increase of GMTs after vaccination for the A/H3N2 and the A/H1N1 strain [43]. Seroconversion was seen only in 3 patients of the late rituximab subgroup against the A/H1N1 strain [43]. Only 6 cases of seroprotection occurred in the rituximab group, of them 5 in the late rituximab subgroup. No correlation was seen between B cell counts and response to influenza vaccination [43].

Influenza-vaccine specific cellular responses were evaluated in RA patients at day 6 after vaccination who had rituximab treatment 6 months ago (post-rituximab group) and in RA patients 6 days before rituximab administration (pre-rituximab group) compared to an RA patient control group, who was not exposed to rituximab [44]. Influenza-specific IgM-secreting B cells were significantly reduced in the post-rituximab group compared to the pre-rituximab group and to the control group [44]. Irrespective of rituximab treatment, the number of influenza-specific IgG- and IgA-producing cells was similar between the groups [44]. No difference was also seen in the vaccine-specific IgM increase between day 0 and 21 after vaccination [44].

Analyzing the cellular and humoral immune response to trivalent influenza subunit vaccine in 29 RA patients treated with rituximab, 17 with DMARDs, mostly methotrexate, and 16 healthy controls, the Interferon-gamma-production by $CD4^+CD69^+$ T cells was similar, but the rituximab-treated RA group showed significantly diminished HI responses (26.4%) compared to the DMARD-treated RA group (68.4%) and healthy controls (47.1%) [45]. That study supported the finding, that an intact T cellular immune response is present in patients treated with rituximab [45].

However, there was a significant lower GMT response to adjuvanted H1N1 influenza vaccination in 5 RA patients with rituximab and 10 RA patients with abatacept compared to 40 healthy controls [46]. Only 25% of patients on rituximab showed a HI ≥ 1:40 at 3 weeks, 6 weeks and 6 months after vaccination, but 45%, 35% and 20% of patients with abatacept and 98%, 95% and 75% in healthy controls [46]. In that study a significant influence of disease type, intensity, type of medication and age were described [46].

In view of that data, several explanations were given to describe the discrepancy between studies showing lower responses to influenza vaccine antigens and almost normal responses under treatment of RA patients with rituximab. A decreased response in some rituximab-treated RA patients to new antigens may be attributed to reduced amounts of B cells or to an increase of regulatory T cells suppressing the immune response [47]. A slower or delayed repopulation of $CD27^+$

memory B cells was described for more than 2 years after rituximab treatment [47]. The sufficient response to influenza vaccination in some rituximab-treated RA patients may be explained by early-differentiated B cells with low-level expression of CD20, which may become the source of antibody production [48]. Despite the complete depletion of B cells in RA patients treated with rituximab, levels of immunoglobulins and pre-existing antibodies against tetanus and pneumococcal-polysaccharide remained stable, which was attributed to the existence of long-lived plasma cells [49]. An explanation for a missing correlation between peripheral B cell numbers and immune response to influenza vaccine [43] may be that the number of B cells within the lymphoid tissue is not correctly reflected by peripheral blood B cell numbers, as despite two cycles of rituximab, $CD19^{+}CD20^{-}$ B cells are able to remain in the bone marrow in RA patients [50]. Higher post-vaccination titers in rituximab-treated patients which had higher pre-vaccination titers, point to the persistence of memory B cells in compartments other than the peripheral blood [24]. Probably, repeated vaccination can be of additional value in these patients to induce better immune responses [24].

Regarding safety aspects, none of the studies [41-46] showed a significant increase of flares, inflammatory parameters or worsening of the disease.

Tocilizumab

IL-6 has been shown to work as a B cell differentiation factor, which promotes activated B cells to produce immunoglobulin [51]. Blocking IL-6 should therefore impair antibody production. Tocilizumab is a humanized monoclonal anti-IL-6 receptor antibody which has been shown to be effective in RA patients with moderate to severe RA who have demonstrated an insufficient response to methotrexate and one or more anti-TNF-α agents [52]. Little experience with vaccinations under treatment with tocilizumab exists from studies in children and young adults with systemic JIA.

Studies of 27 patients with systemic JIA showed a similar efficacy 4 to 7 weeks after influenza vaccination with no influence of duration of tocilizumab therapy compared to 17 healthy controls [53]. In that study, no severe adverse events or disease exacerbation was recorded after the influenza vaccination [53]. However, one case of disease exacerbation after influenza vaccination was reported in a single patient with systemic JIA receiving tocilizumab [54].

Assessing the impact of tocilizumab therapy on the HI antibody response to influenza vaccination for the A/H1N1 and A/H3N2 strains in patients with RA, both groups, the group treated with tocilizumab alone (n=62) and the group treated with tocilizumab and methotrexate (n=49) reached postvacccination seroresponse rates (seroconversion or ≥ 4-fold increases in antibody titers whose pre-vaccination titers were ≥ 1:10) greater than 40% and seroprotection rates (antibody titers ≥ 1:40) greater than 70% [55]. Methotrexate alone seemed to have a negative impact on GMTs, although protection responses were not different from the other groups [55].

Explanations for almost normal immune responses to vaccinations under tocilizumab may be, that IL-6 is not the sole factor participating in antibody production by B cells and that IL-6 signaling may not completely inhibited in lymphoid tissues, which allows to ongoing antibody production to specific antigens.

Other vaccinations

Despite significantly increased risks of infectious complications of vaccine-preventable diseases, experiences with other vaccinations than influenza and pneumococcal vaccines are rare in RA patients receiving immunotherapies.

In a controlled study, 64 RA patients on rituximab and methotrexate were compared to 26 RA patients on methotrexate alone regarding their response to tetanus toxoid vaccination [56]. Both groups showed similar titer increases, similar numbers of patients with non-protective titers and no differences in GMTs prior to vaccination and 4 weeks after vaccination [53].

Regarding hepatitis A and B vaccination, efficacy and safety was demonstrated in children with JIA [57] and RA patients on methotrexate and other conventional DMARDs [58], but no data exist from RA patients receiving immunotherapies. Although human papillomavirus vaccination should be considered in young women with RA, no experience with human papillomavirus vaccination was reported in RA patients. Similarly, no data exist for cholera, diphtheria, pertussis, meningococcal, poliomyelitis, rabies and tick-borne encephalitis vaccinations in RA patients. RA patients on immunotherapies planning to travel abroad should receive their vaccinations according to general rules, except for live-attenuated vaccines, such as Bacillus Calmette-Guérin (BCG), oral poliomyelitis, oral typhoid fever and yellow fever vaccines, due to expected life-threatening dissemination of the attenuated pathogens [23].

Among RA patients an increased risk of herpes zoster was described [59,60]. A large prospective cohort study investigated the long-term safety and effectiveness of anti-TNF-α therapy in the treatment of 3,266 RA patients (adalimumab 1,423 patients, etanercept 1,252 patients, infliximab 591 patients) compared to 1,774 RA patients on conventional DMARDs [59]. A significantly higher incidence rate of herpes zoster was observed in RA patients receiving infliximab/adalimumab (11.1 per 1,000 patient-years) or etanercept (8.9) compared to RA patients on conventional DMARDs (5.6) [59]. A significant reduction of postherpetic neuralgia was demonstrated in older adults vaccinated with a high-antigen containing live-attenuated herpes zoster vaccine [61]. However, poor experience with the herpes zoster vaccine exists for RA patients in unease of severe adverse effects and dissemination of the vaccine-type varicella-zoster virus. Based on expert opinions, glucocorticoids at prednisone-equivalent doses up to 20 mg/day, low doses of methotrexate (<0.4 mg/kg/week), azathioprine (<3.0 mg/kg/day) and 6-mercaptopurine (<1.5 mg/kg/day) were considered to be safe and do not define a contraindication against herpes zoster vaccination [62], but the vaccine is not recommended for RA patients with biologic treatments [24]. In a large cohort study among 44,115 patients with autoimmune diseases aged ≥ 50 years, 551 patients received the herpes zoster vaccine, of them 32 patients were treated with anti-TNF-α therapy at the time of vaccination and 47 patients used biologics at some time within 30 days before and after vaccination [62]. None of these patients developed herpes zoster in the 30 days after vaccination [62].

Regarding the general problem with live-attenuated vaccines in immunocompromised patients, studies of children with autoimmune rheumatic diseases on methotrexate, low dose glucocorticoids or anti-TNF-α therapy receiving immunological booster with live-attenuated measles, mumps, rubella or varicella vaccination reported no severe adverse events [63,64].

Discussion

However, researchers, rheumatologists and physicians taking care

of patients with RA on immunotherapies are faced with several problems regarding vaccination studies and deduction of recommendations (Table 2). An EULAR expert committee used a Delphi voting system for addressing 8 key questions and 13 recommendations for vaccinations in patients with autoimmune inflammatory rheumatic diseases [23]. In the initial work-up of patients, particularly before starting immunsuppressive or immunomodulatory therapies, the vaccination status should be assessed [23]. Ideally, vaccines should be administered during stable disease [23]. Vaccinations can be administered during the use of DMARDs and immunotherapies [23]. However, awareness should be given to the type of vaccine used (e.g. adjuvanted or non-adjuvanted, conjugated or polysaccharide, non-live-attenuated or live-attenuated vaccines) and a delayed, lower or faster declining immune response has to be considered.

Particularly, the administration of live-attenuated vaccines displays a challenge in potentially immunsuppressed patients. Herpes zoster vaccination is a promising strategy to avoid herpes zoster associated complications, such as postherpetic neuralgia [61], and may be considered in cases of low to moderate immunosuppression according to the Advisory Committee on Immunization Practices (ACIP) [65].

Inactivated influenza and 23-valent polysaccharide pneumococcal vaccinations are strongly recommended for patients with autoimmune inflammatory rheumatic diseases. Data regarding efficacy and immunogenicity of influenza and pneumococcal vaccines in patients with RA receiving immunotherapy with anti-TNF-α agents, blockade of the CD80/CD86:CD28 co-stimulatory signal or of IL-6 or depletion of B cells are rare and often conflicting. Crucial problems in the interpretation of data from studies in RA patients vaccinated against influenza and pneumococcal disease are the impaired comparability of studies due to different study designs and type of vaccines used, different health states among RA patients, heterogeneity in treatments including concomitant therapy with conventional DMARDs and glucocorticoids in addition to biological agents. Particularly in studies from the past, there is a selection of cases which may suffer from a more severe disease where several conventional DMARDs failed and new approaches with biologic agents are undertaken. But there may be also a change over time in prescription habits and a more courageous use of immunotherapies in patients in whom the first DMARD (usually methotrexate) was not successful to induce remission. Different study designs with different time points of antibody evaluation and different study end points (e.g. GMTs, the relative increase of antibody titers, protective antibody titers) do not allow to compare the studies to each other. Further problems are small numbers of RA patients studied and often the inclusion of various biologic agents with or without conventional DMARDs into one group compared to different control groups, consisting of randomly taken healthy individuals or RA patients on conventional DMARDs with or without methotrexate or glucocorticoids on different dosages. However, no trend to lower vaccine responses could be deduced from studies including larger numbers of patients (Table 1). Also, in most studies the time on immunotherapies and the timing of vaccination is not considered in the interpretation of results. Conflicting data were presented for influenza vaccination, showing an influence of timing regarding treatment of rituximab [43,44] or not [42]. Prevaccination antibody titers may also influence the results [16].

An extrapolation of immune responses from one influenza vaccine to another may be not permitted, as so far no clear benefit of adjuvanted or non-adjuvanted influenza vaccines or different antigen preparations could be deduced from studies.

Age remains an important confounder in vaccine studies, as lower, delayed or faster decreasing humoral immune responses are reported in elderly, healthy individuals [66]. Influence of age on responses to the pneumococcal vaccine was also seen in RA patients treated with infliximab and glucocorticoids [30]. Aspects of immunological aging [66] are mostly not considered in the evaluation of antibody titers and antibody maintenance in RA patients on immunotherapy.

A study in ovarectomized mice showing lower antibody levels to influenza vaccine than mice receiving estradiol suggested an influence of gender and hormone status on the specific immune responses [67]. Interestingly, hormonal aspects were mostly covered by factors of disease activity as shown in a study of hormone replacement therapy in women with RA [68]. Hormonal replacement therapy was not associated with an altered response to influenza vaccination [68].

Also, the effect of lifestyle factors, such as alcohol consumption and smoking, on the immune response should be considered when conducting vaccination studies. Smoking has been shown to be a predictor of an impaired immune response to pneumococcal conjugate vaccine antigens 23F and 6B in RA patients on methotrexate [69].

Additionally, assays used to assess the antibody response differ between the studies and protective antibody titers described for healthy volunteers may not necessarily correlate with protection in RA patients. It remains widely unclear how long protective antibody titers exist in patients with RA and no recommendations are collated for antibody titer controls and booster intervals.

An increase of vaccine-related adverse events did not appear in studies considering safety aspects of vaccines in RA patients on immunotherapies compared to RA patients on DMARDs alone. Unfortunately, these studies are generally underpowered to study adverse events as a primary outcome and therefore not conclusive [23,24].

Conclusion

Patients with RA are at higher risk to suffer from morbidity due to vaccine-preventable diseases and, thus, display an important target population to receive vaccines for protection from infectious complications. There have been only a few studies focusing on the administration of vaccines in RA patients with immunotherapy.

Study aspects	Individual aspects	Laboratory aspects
• Study design (cross-sectional, cohort studies; placebo controlled, randomized, double-blind; prospective or retrospective; investigational or non-investigational, observational studies) • Inclusion and exclusion criteria • End points (GMTs, increase of titers, protective titers) • Heterogeneity of compared groups (healthy controls or RA patients) • Heterogeneity in vaccine preparations (adjuvanted or non-adjuvanted; polysaccharide or conjugated; containing antigens) • Timing of vaccination	• Health state • Disease course • Severity of disease • Co-morbidities • Age • Gender and hormonal changes • Life-style factors (e. g. smoking, alcohol) • Heterogeneity in use of immunotherapies • Duration of immunotherapies • Heterogeneity in use of conventional DMARDs and glucocorticoids	• Time point of antibody assessment • Pre-vaccination titers • Assays used (sensitivity and specificity) • Specificity of antigens used in assays • Definition of response and protection

Table 2: Influencing factors for interpretation of immunogenicity and efficacy in vaccine studies in RA patients on immunotherapies.

Overall, antibody response rates against influenza or pneumococcal disease appeared to be only slightly lower than expected in healthy individuals.

The disease itself, its cause and severity may be a compromising factor in the generation of a sufficient humoral immune response to the vaccines. The response rates to specific vaccine antigens also roughly depend on which anti-TNF-α agents as well as other immunomodulatory drugs used. Also, the concomitant use of conventional DMARDS, particularly methotrexate and glucocorticoids, seems to influence the antibody response.

The type of vaccine may be considered when taking plans for the vaccination of RA patients. So far, no clear recommendations for the choice of adjuvanted or non-adjuvanted influenza vaccines or polysaccharide or conjugate pneumococcal vaccines can be deduced from studies. The hypothesized better response to T cell dependent conjugate vaccines has to be investigated, also whether vaccines with higher antigen doses as proposed for elderly individuals [66] are more efficient. The hypothesized risk for adverse reactions after administration of live-attenuated vaccines, e.g. herpes zoster vaccination, in RA patients receiving immunotherapies has to be clarified [7]. Certainly of interest are immunogenicity and safety aspects of live-attenuated nasal influenza vaccines in immuncompromised RA patients, but have been so far only investigated in children with cancer [70,71] and HIV-infected patients [72].

Applying a Delphi voting among rheumatologists and experts in the field, recommendations for vaccinations in patients with autoimmune inflammatory rheumatic diseases were established emphasizing the assessment and the completion of the vaccination status before initiation of immunomodulatory therapies or during stable disease [23]. Long-term data are missing for the maintenance of protective antibody titers in RA patients as a faster decline of antibodies was assumed for patients with rheumatic diseases [73]. If this could be confirmed for certain vaccines, routine controls for antibody titers and specific strategies for earlier re-vaccination might be scheduled for patients with RA.

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