Vaccine Responses in Patients with Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is a systemic autoimmune disease that is associated with immunologic alterations in T cells and B cells. Moreover, many of the agents used in RA patients are potentially immunosuppressive. Thus, the underlying disease and treatment may both increase the susceptibility to infections and decrease vaccine responses. With the growing use of aggressive therapies for RA, including anti-tumor necrosis factor agents and newer biologic therapies such as rituximab and abatacept, an increasing concern will be that patients may not respond to conventional vaccination. Further prospective studies on response to vaccination are needed to answer this important public health question. Nevertheless, it is already clear that vaccination does induce response in many patients. Unfortunately, vaccination is underutilized in RA patients and needs to be aggressively promoted.

Introduction

Rheumatoid arthritis (RA) has been shown to have drastic effects on the immune system. Patients with RA are known to have changes in T cells, such as an impaired ability to react to antigens [1,2], an increased peripheral blood CD4/CD8 ratio, and signs of activation as evidenced by the presence of soluble interleukin-2 receptors in peripheral blood. In addition, the T-cell receptor repertoire has been shown to be oligoclonal, which suggests on one hand antigen selection and the other hand restriction of the repertoire. There is also a decline in thymic output of T cells. Thus, T-cell receptor rearrangement excision circles measured from T cells from RA patients were substantially reduced compared with healthy controls [3]. Telomere lengths were also noted to be prematurely shortened in peripheral blood T cells of RA patients; they were equivalent to healthy controls 20 years older [3,4]. This premature aging of T cells in RA may have profound effects on vaccine responses, which are well know to decrease with aging [5,6]. Finally, the function of regulatory T cells (CD4+, CD25+) may be abnormal in active RA patients with a lack of suppression of effector T cells [7].

The multiple immunologic effects of the disease process may partly explain why RA patients are at increased risk of infections [8]. In a population-based study, age, extra-articular RA involvement, leukopenia, and other comorbidities appeared to be independent risk factors for infection [9]. In the same study, corticosteroid therapy increased infection risk ($P < 0.004$), but interestingly on multivariate analysis, other medications did not. However, this study predated widespread use of anti-tumor necrosis factor (TNF) agents. In a cohort study, risk for hospitalization with pneumonia was significantly increased in a dose-dependent fashion with prednisone use but was not increased for anti-TNF therapy or methotrexate [10••]. This finding conflicts with a recent meta-analysis of randomized, double-blind, placebo-controlled trials, which did show an increased risk of infection in RA patients who were on adalimumab or infliximab [11••].

Despite evidence that RA patients are immunocompromised, potentially life-saving preventive measures, such as pneumococcal and influenza vaccination programs have been grossly underutilized (under 40%), whereas screening for other health-related issues such as cholesterol and blood pressure are approximately 90% [12]. In the United States, pneumococcal infections are responsible for 3000 cases of meningitis, 50,000 cases of bacteremia, and over 500,000 cases of pneumonia each year [13]. Approximately 40,000 deaths occur each year due to invasive pneumococcal infection, of which half are believed to have been preventable with adequate vaccination [13]. Influenza causes approximately 36,000 deaths per year in the United States [14•], and over 90% of deaths are individuals 65 and older. Although prevention rates vary depending on the age of the patient and the degree of matching between the vaccine and the virus, vaccination drastically reduces hospitalizations, death rate, and sick days [14•]. The purpose of this

review is to summarize the available data on vaccination effectiveness in RA patients who are on numerous immunosuppressive agents and to discuss specific immunization recommendations in this population.

Methods

An Ovid Medline search from 1966 to the present was performed using the search terms corticosteroids, glucocorticoids, methotrexate, anti-TNF, etanercept, adalimumab, infliximab, abatacept, and rituximab. Each of these terms was cross-referenced with hepatitis B, pneumococcal, influenza, and vaccination. All search terms were limited to English language journals. The American College of Rheumatology and European League of Arthritis and Rheumatism national meeting abstracts were similarly searched for all available online abstracts (European League of Arthritis and Rheumatism, 2001-2006, and American College of Rheumatology, 2002-2006) using the search terms hepatitis B, influenza, pneumococcal/pneumococcus, immunization, and vaccination.

Responses to Specific Vaccines

Pneumococcal vaccination

Streptococcus pneumoniae structurally has a polysaccharide capsule that prevents phagocytosis by neutrophils. Antibodies to capsular polysaccharides opsonize the organism and confer immunity. Pneumococcal polysaccharides do not require T cells to induce antibody production and are therefore termed T-independent (TI) antigens. TI antigens are further classified as TI-1 if they are able to elicit an adequate immune response in young children (< 2 years old) or CBA/2 mice. Examples of TI-1 antigens include lipopolysaccharide, and *Brucella abortus*. TI-2 antigens are TI antigens to which young children do not make adequate antibody responses. TI-2 antigens include the capsular polysaccharides of *S. pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* [15]. The antibody response of infants to TI-2 antigens can be greatly enhanced by conjugating capsular polysaccharides to T-cell–dependent antigens such as diphtheria cross-reactive material (an inactive toxin) or tetanus toxoid. These conjugate vaccines convert the TI-2 response to a T-dependent response, and elicit strong T-cell activation, isotype switching, and memory B-cell production, thereby allowing boosting.

Different serotypes of *S. pneumoniae* have been more implicated in invasive disease in various parts of the world. In the United States and Canada, the seven most common serotypes in descending order are 14, 6, 19, 18, 23, 9, and 4 [16]. Initial vaccines were directed at 14 or 23 polysaccharide antigens. Although clinically effective in older children and adults, several limitations to these vaccines restricted their clinical utility. Elderly patients and young children did not respond to these vaccines. Response rates in the conjugated pneumococcal vaccine in healthy young children varied depending on the serotype, ranging from 100% for serotype 14, 18C, and 23F to 84.6% for 19F [17]. Lower response rates were detected in immunocompromised patients such as Hodgkin's disease patients within 2 years of treatment and HIV-positive patients [13,16].

Recent literature assessing the efficacy of pneumococcal vaccine in RA patients has produced a variety of results (Table 1). Kapetanovic et al. [18•] found that patients on methotrexate alone or methotrexate plus anti-TNF therapy had lower response rates to serotype 23F and 6B in the 23-valent polysaccharide vaccine compared with controls and patients on anti-TNF therapy alone. O'Dell et al. [19] found a lower response rate with methotrexate. Elkayam et al. [20] found that a significant subset of patients on anti-TNF therapy did not respond as well as compared with healthy controls. When comparing RA and ankylosing spondylitis patients on infliximab, 3 mg/kg, and etanercept, 25 mg twice weekly, to RA patients without TNF blockade, a statistically significant lower response rate was seen in the anti-TNF group to serotype 23F but not to six other serotypes [21].

Similar results are seen in juvenile idiopathic arthritis (JIA), as reported by Kasapcopur et al. [22]. In this study, 50 JIA patients in remission and 24 healthy controls were immunized to the 23-valent pneumococcal vaccine. Although the antibody response rate was equal between the two arms, there was a statistically significant lower antipneumococcal capsular immunoglobulin (Ig) G in patients on methotrexate and corticosteroids. Visvanathan et al. [23] did not detect a significant difference in polysaccharide vaccine response when comparing patients on low-dose infliximab, 3 mg/kg, with methotrexate; high-dose infliximab, 6 mg/kg, with methotrexate; and placebo with methotrexate. Finally, a randomized, double-blind, placebo-controlled trial of 208 patients by Kaine et al. [24] found no significant difference between response rates and antibody concentrations in RA patients receiving adalimumab (n = 99) in three doses (80 mg on day 1 and 40 mg on days 15 and 29) and placebo (n = 109). Vaccine response rates were checked on day 36 and defined as greater than a twofold increase from baseline antibody titer in more than three of five antigens measured.

The best study evaluating the effects of therapy on vaccine response was a relatively large multicenter, randomized, placebo-controlled trial studying the effect of etanercept to 23-valent pneumococcal vaccine in psoriatic arthritis patients. In this study, 184 patients were randomly assigned to placebo or etanercept treatment for 4 weeks but were continued on previous medications for RA. Adequate response to five polysaccharide antigens (9V, 14, 18C, 19F, and 23F) was defined as a greater than twofold increase in antibody titers in more than three antigens. Using logistic regression analysis, methotrexate use was a predictor of poor response (RR = 2.11) [25], whereas anti-TNF use did

Table 1. Pneumococcal vaccination response in RA patients

Study	Patients; controls, *n*	Medication, *n*	Assay; response measured	Result
Kapetanovic et al. [18•]	149 (RA); 47	48 (etanercept), 64 (INF), 37 (MTX); 50 anti-TNF patients were also on MTX	ELISA; twofold increase in levels of serotypes 23F and 6B	MTX had significantly lower response compared to anti-TNF, anti-TNF/MTX, and healthy controls
Kasapcopur et al. [22]	50 (JIA in remission); 24	38 (MTX), 28 (corticosteroids), others unknown	ELISA; twofold increase in antibody titers	No difference in response rates but blunted antibody titers with MTX and corticosteroids
Kaine et al. [24]	99 (RA anti-TNF); 109 (RA non–anti-TNF)	99 (adalimumab, 80 mg day 1 and 40 mg days 15 and 29)	ELISA; > twofold increase in antibody titers	No difference in response rate or protective antibody rates
Visvanathan et al. [23]	56 (RA anti-TNF); 14 (RA on MTX)	20 (INF 3 mg/kg plus MTX), 36 (INF 6 mg/kg plus MTX), 14 (placebo plus MTX)	Unknown; twofold increase in 6 of 12 serotypes	20% INF/MTX 3 mg/kg; 25% INF/MTX 6 mg/kg; 21.4% MTX; no difference between groups
Elkayam et al. [21]	11 (RA), 5 (AS), both groups on anti-TNF; 17 (RA on other medication)	12 (INF 3 mg/kg), 4 (etanercept in treatment group)	ELISA; twofold rise in antibody titers of 7 serotypes, or > 1 μg/mL increase	Anti-TNF group had statistically lower response rates (13%) to 23F compared to controls (53%)
Elkayam et al. [20]	42 (RA); 20	16 (NSAIDs), 26 (MTX), 24 (prednisone < 10 mg/day), 5 (prednisone > 10 mg/day) in RA group; none in controls	ELISA; twofold increase in measured geometric mean concentrations of 7 serotypes	100% of controls responded but 14/42 RA did not respond at all or responded to only 1 serotype
O'Dell et al. [19]	20 (RA on MTX); 20 (RA not on MTX)	MTX group mean dose was 13 mg/wk	ELISA; percentages of 3, 7F, 9N, and 14 levels > 300 μg/mL	MTX 55% converted vs 77% non-MTX ($P = 0.03$)

AS—ankylosing spondylitis; ELISA—enzyme-linked immunosorbent assay; INF—infliximab; JIA—juvenile idiopathic arthritis; MTX—methotrexate; NSAID—nonsteroidal anti-inflammatory drug; RA—rheumatoid arthritis; TNF—tumor necrosis factor.

Table 2. Influenza vaccine response in RA patients

Study	Patients; controls, *n*	Medication, *n*	Vaccine administered	Assay; response measured	Result
Fomin et al. [30•]	82 (RA); 30	56 (MTX), 22 (INF), 5 (etanercept), 44 (combo)	B/Hong Kong/330/2001 (HK); A/Panama/2007/1999 (PAN); A/New Caledonian/20/1999 (NC)	Fourfold increase in HI titers, or rise from < 1/40 to ≥ 1/40	67% in RA vs 87% in controls for HK, no $P < 0.05$; no difference with PAN and NC
Del Porto et al. [35]	10 (RA); 20 (10 nonvaccinated RA patients)	All treated with < 10 mg prednisone plus either MTX or cyclosporine, two patients with anti-TNF	A/New Caledonia/20/99; A/Moscow/10/99; B/Hong Kong/330/2001	HI titers, seroconversion (fourfold increase in HI titers); protective antibody concentration of > 1:40	No difference between vaccinated RA and vaccinated healthy controls
Kapetanovic et al. [18•]	149 (RA, in three different arms); 18	62 (anti-TNF: etanercept or INF), 50 (anti-TNF and MTX), 37 (MTX only)	Unknown	HI titers, > fourfold increase in titers; protective titers of > 1:40	MTX arm had significantly better response compared to other two RA arms and healthy controls
Kaine et al. [24]	99 (RA anti-TNF); 109 (RA non–anti-TNF)	99 (RA received adalimumab, 80 mg day 1 and 40 mg day 15 and 29)	Unknown	HI titers, fourfold increase in HI titers from baseline in > 2 of 3 antigens; protective antibody concentration of > 1:40	No difference in response rate or protective antibody concentration rates
van der Bijl et al. [31]	113 (RA); 18 (age- and gender-matched)	65 (etanercept, INF, or adalimumab), 48 (other agents)	Influvac 2003/04; unknown subunits	HI assay; protective titers defined as ≥ 1/40	H3N2 response was lower in anti-TNF group vs control ($P < 0.05$)
Chalmers et al. [34]	126 (RA); 64	14 (MTX), 8 (prednisone > 7.5 mg), 19 (prednisone < 7.5 mg)	A/Taiwan/1/86 (H1N1); A/Beijing/353/89 (H3N2); B/Panama/45/90	Fourfold increase in titers in HI titers, or rise from < 1/40 to ≥ 1/40	No significant difference in response between groups
Malleson et al. [36]	33 (juvenile chronic arthritis); 10	21 (NSAID), 7 (prednisone), 9 (other)	A/Taiwan/1/86 (H1N1); A/Beijing/353/89 (H3N2); B/Panama/45/90	Fourfold increase in HI titers, or rise from < 1/40 to = 1/40.	No significant difference in response between groups
Herron et al. [33]	20 (SLE), 17 (RA), 8 (DJD), 17 (other); 32	9 of 17 RA (prednisone, average dose 10 mg)	A/New Jersey/76 (H1N1); A/Victoria/75 (H3N2)	HI assay; mean geometric titers	No difference in response rates between groups

DJD—degenerative joint disease; HI—hemagglutination inhibition; INF—infliximab; MTX—methotrexate; NSAID—nonsteroidal anti-inflammatory drug; RA—rheumatoid arthritis; SLE—systemic lupus erythematosus; TNF—tumor necrosis factor.

not affect vaccine response. In summary, although some data exist on the effect of immunosuppressive agents in RA patients on pneumococcal vaccine immune responses, the best study with these agents is in psoriatic arthritis. The results of this study suggest that methotrexate decreases response but etanercept does not. Extrapolation of these results to RA would seem to be reasonable, but data in RA would be preferable.

The published literature in RA varies in terms of the primary endpoint used, the assay utilized to measure the primary endpoint, and the medications studied. Most RA studies were fairly small, and none were randomized. However, the administration of these vaccines did not result in disease exacerbation or other adverse reactions compared to placebo. In addition, all the studies found a large number of patients who developed increased antibody titers, although the amount of increase was variable. Functional assays, such as opsonophagocytic assays, have not been studied, and they may be important in patient groups such as older individuals [26]. Moreover, how well this increase in antibody titer predicts protection from infection in RA patients is unclear. Despite these limitations, the pneumococcal polysaccharide vaccine should be given to all RA patients, and readministered every 5 to 10 years as per recommendations for other immunocompromised patients. Ideally, immunization would occur prior to initiating treatment with methotrexate or new biologics rituximab and abatacept. A role for the conjugate pneumococcal vaccine is unclear and should be explored.

Influenza vaccination

The influenza virus is an enveloped, single-stranded RNA virus that contains a nuclear capsid and lipoprotein envelope. This envelope is studded with hemagglutinin and neuraminidase, which are critical for infection and are the major targets for protective antibody responses. Antihemagglutinin antibodies neutralize virus from infecting the host cell and prevent the development of influenza. In contrast, antineuraminidase antibodies are more effective in reducing viral shedding and may play more of a role in preventing clinical disease rather than infection. The inactivated influenza vaccine is a trivalent vaccine containing influenza A (H1N1, H3N2) and influenza B strains that are predicted, based on epidemiologic surveillance, to be prevalent the following influenza season. The live influenza vaccine should not be used in immunocompromised patients and has not been studied in RA.

Efficacy in healthy individuals varies depending on the degree of matching between the strains in the vaccine and the prevailing virus. There typically is a 70% to 90% seroconversion rate if a match occurs between the vaccine and viral strains [27]. Elderly individuals had a lower response rate of 58% in a prospective controlled trial [6]. In addition, peak levels are obtained later, and immunity wanes faster in elderly individuals than in younger adults. Despite the blunted immune response, one meta-analysis showed reductions in hospitalization for influenza pneumonia by 33%, in mortality by 50%, and in influenza-like illness by 33% among community-living elderly individuals after they obtained the influenza vaccine [28]. Studies in elderly patients in nursing homes have shown similar results [29].

The influenza vaccination response in RA patients has also had variable results (Table 2). Fomin et al. [30•] compared 82 RA patients on various medications including methotrexate, infliximab, etanercept, prednisone (average dose 8 mg), and hydroxychloroquine to healthy controls. Primary outcomes included the percentages of patients that showed a positive response 6 weeks after vaccination. Response was defined as a fourfold increase in hemagglutination inhibition titers or a rise from a nonprotective level (< 1/40) to (≥ 1/40). No significant difference was seen in response to the two influenza A strains, but with Hong Kong influenza B, 67% of RA patients responded compared with 87% of healthy controls ($P = 0.004$). No correlation was found with medication utilization, sex, age, disease duration, or disease activity. Similarly, a prospective study by van der Bijl et al. [31] found a diminished response to H3N2 on patients with anti-TNF agents (infliximab, adalimumab, or etanercept) compared with RA patients not on anti-TNF therapy and healthy controls. Paradoxically, a more recent abstract by Kapetanovic et al. [32] found a statistically significantly higher response rate to RA patients treated with only methotrexate compared with those RA patients receiving anti-TNF therapy alone or in combination with methotrexate.

However, decreased response in RA patients was not found in some other studies. The first study done to assess influenza vaccine efficacy was by Herron et al. [33]. In the study, 62 patients with systemic lupus erythematosus or RA were compared to 32 healthy controls, and the researchers found no difference in seroconversion rates. Chalmers et al. [34] stratified 126 RA patients into three groups: 1) RA patients on "routine medications" such as nonsteroidal anti-inflammatory drugs, gold, prednisone less than 7.5 mg, and penicillamine without prior influenza vaccination; 2) RA patients on "routine medications" with prior vaccination; and 3) RA patients on a variety of immunosuppressive therapy such as methotrexate, cyclosporine, azathioprine, and prednisone greater than 7.5 mg. These patients were compared to age- and sex-matched healthy controls. In this study, RA patients on immunosuppressive medications responded just as well to the vaccine as the healthy controls. Moreover, when combining all RA patients, no significant difference was observed in influenza response rates compared with the control group. Del Porto et al. [35] found no difference in influenza vaccine response rates when comparing RA patients with low disease activity scores (< 4) to healthy controls. Recently, a randomized, double-blind, placebo-controlled trial showed no difference in response rates and protective antibody concentration rates in RA patients receiving adalimumab for three doses compared to RA

controls [24]. Similar results were found in a prospective study evaluating children with chronic arthritis compared to healthy controls [36].

Thus, aside from a diminished response to one of the three valents in a few studies, a relatively good overall response to the influenza vaccine appears to exist in RA regardless of medication use. Previous concerns over the safety of the vaccine in RA patients have largely been disproved. Therefore, all patients with RA should receive yearly vaccines without special consideration. Importantly, US Centers for Disease Control and Prevention guidelines recommend the administration of antivirals as chemoprophylaxis in settings of influenza outbreaks with susceptible populations who may have poor vaccine responses (eg, elderly individuals in nursing homes and immunosuppressed individuals) [13].

Hepatitis B

Hepatitis B is a double-stranded DNA virus with an outer envelope containing hepatitis B surface antigen (HBsAg). This antigen is the target of neutralizing antibody in the host and the component of vaccines that trigger the protective immune response. Antibody production is inherently a B-cell function, but this process is T helper–dependent in the case of hepatitis B. Originally, vaccine preparations were derived from the plasma of patients infected with hepatitis B that were purified and denatured to produce inactive but immunogenic HBsAg particles. Recombinant DNA vaccines have now largely replaced plasma vaccines due to ease of production.

Efficacy of the recombinant DNA vaccine has been reproducibly reported to be greater than 90% in infants, children, adolescents, and adults younger than 40 years old. After that age, vaccine responses gradually decline to levels of 60% to 75% after age 60 [37]; due in part to the age-related decline in naïve CD4 T cells [5]. Immunocompromised patients such as HIV patients have suboptimal responses to vaccination [38].

Immunization studies in RA patients have shown a 68% protective response rate as defined by enzyme-linked immunosorbent assay titers of antibodies to HBsAg greater than or equal to 10 IU/L [39]. These patients were on numerous agents, but none were on anti-TNF therapy or newer agents such as rituximab or abatacept. Another prospective control study evaluated children with JIA and found no significant difference in seroconversion rate between healthy controls and the children with JIA [40]. No difference was found when comparing children on glucocorticoids and methotrexate to children not taking immunosuppressive medications. Neither of these studies showed any adverse events over the controls, disputing earlier findings that RA flares may be linked to hepatitis B vaccination [41,42]. Therefore, patients with RA should be vaccinated as per prior guidelines without special consideration. Vaccine response rates in patients on newer agents have not been established but studies are currently ongoing.

Effects of Newer Biologic Therapies on Vaccine Responses

Anti-TNF agents

The biologic consequences of treatment with anti-TNF antibodies (infliximab and adalimumab) versus chimeric decoy receptors (etanercept) on vaccine responses may be quite different since the latter binds both TNF and lymphotoxin-α. Although both TNF and LT have critical functions in the interplay between antigen-specific B cells and T cells and dendritic cells within the microenvironment of the secondary lymphoid organs, LT plays a dominant role in the development and maintenance of organized lymphoid tissue [43]. The ability to mount an effective immune response to vaccination depends on the microarchitecture of the B-cell follicle, germinal center, and marginal zone. Thus, studies of mice deficient in LT-α or β reveal deficiencies in primary, secondary, and memory humoral immune responses. Deficiency of TNF-α or either TNF receptor results in grossly normal splenic and lymph node microarchitecture but these mice fail to form isotype-switched Ig responses after immunization with T-dependent antigens [44].

A detailed understanding of how anti-TNF influences vaccine responses in humans is lacking. However, we have recently found that anti-TNF treatment of RA patients has profound effects on B-cell homeostasis. Thus, RA patients on etanercept have a reduced proportion of peripheral CD27+ B memory cells, a dramatic reduction in lymphoid germinal center B cells, and reduced follicular dendritic cell networks [45]. Since follicular dendritic cells are the major cell responsible for antigen trapping and B-cell selection within the germinal center, their elimination would be expected to lead to compromised immunologic memory and affinity maturation of the humoral immune response [46]. Vaccination studies are underway in our lab to address this directly.

Rituximab

Rituximab has emerged as another potential therapeutic option for a number of rheumatologic conditions. The drug was recently approved by the US Food and Drug Administration for the treatment of anti-TNF–failure RA [47,48]. Specifically, it targets CD20 on pre-B cell and mature B cell by antibody-dependent cellular cytotoxicity, complement-directed cytotoxicity, and induction of apoptosis. B-cell depletion by rituximab has not resulted in lower Ig levels or antibody levels, because plasma cells do not express CD20. However, secondary responses to vaccination with tetanus toxoid and polio were found to be inhibited in one study of nine patients with low-grade relapsed lymphoma [49]. Primary responses to vaccination with hepatitis A virus and keyhole limpet hemocyanin were not seen before or after starting rituximab. Primary and secondary antibody responses to neoantigens such as phiX174 were severely inhibited in chronic renal failure patients on rituximab compared with other chronic renal

failure patients and healthy controls [50]. Preliminary research comparing 29 RA patients on conventional RA therapy, eight RA patients on rituximab, and 21 healthy controls found a diminished response rate to only one of three influenza trivalents in the rituximab arm [51].

Although further study of vaccine responses in RA patients on rituximab is necessary, there is reason to believe B-cell depletion will decrease both primary and secondary vaccine responses. Therefore, it seems prudent for patients to receive vaccinations before instituting therapy. However, further study of optimal timing for both primary and secondary vaccinations relative to B-cell reconstitution are clearly warranted, given that new vaccinations may be necessary depending on the clinical situation. This issue will be important in RA, in which repeated courses of rituximab will likely be necessary for disease control [52]. A unique situation also arises with yearly influenza vaccination. In patients at high risk and in whom protective responses to vaccines are in question, it may be warranted to begin prophylactic antivirals to protect from influenza infection. Thus, prophylactic antivirals may need consideration in patients treated with rituximab.

Abatacept

Another potential mechanism whereby drugs may inhibit vaccine responses is via blockade of T-cell costimulatory signals. One such example is abatacept, a chimeric protein of cytotoxic T-lymphocyte–associated antigen (CTLA)-4 and IgG Fc, which binds to CD80 and CD86, thereby preventing CD28 signaling and T-cell activation. Studies to assess humoral responses with abatacept are currently limited. However, patients with psoriasis vulgaris receiving abatacept were seen to have an inhibited immune response after immunization with the T-cell–dependent antigen phiX174. This inhibition appeared roughly dose related (1–50 mg/kg). Similar inhibition was found after secondary immunization with keyhole limpet hemocyanin. Interestingly, this effect disappeared at the 50 mg/kg dose [53]. The authors hypothesized that the higher dose may favor lower affinity binding to CD80 and CD86 and thereby paradoxically reduce the blocking efficacy. It may also block the in vivo inhibitory signaling via CTLA-4 Ig, thus having a paradoxical effect. Recently, preliminary evidence suggests no impairment of responses to either the tetanus vaccine or to the 23-valent pneumococcal vaccine after a single dose of abatacept [54].

Further studies to assess vaccine responses must be conducted before any firm conclusions can be drawn on the effect of abatacept therapy. However, at this point, sufficient evidence exists to prompt concern that abatacept therapy prevents adequate vaccine responses.

Conclusions

Currently, no randomized controlled trials have examined responses to various vaccines in RA patients. However, preliminary evidence suggests that some of the newer biologic agents, especially abatacept and rituximab, may inhibit protective antibody production with vaccination. In addition inhibition may occur with other agents such as methotrexate, corticosteroids, and anti-TNFs, but current evidence does not conclusively support this possibility. Increased adverse events did not seem to occur in the vaccinated RA patients as compared with healthy controls. It is important to immunize these patients and to continually maintain updated immunization records as standard practice. Immunization prior to starting immunosuppressive therapy is desirable, especially with antipneumococcal polysaccharide vaccines, but this strategy may not always be possible. Prophylaxis with antiviral medications should be considered during outbreaks of influenza for patients unlikely to respond to influenza vaccination. Studies using standard vaccine and immunization schedules are needed, especially with some of the newer biologic agents. In addition, innovative immunization practices such as conjugate pneumococcal vaccines and new adjuvants may improve vaccine responses in this population and should be developed.

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