Immunity against Varicella Zoster virus in patients with systemic lupus erythematosus or rheumatoid arthritis

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Abstract

Patients with systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA) are at high risk for developing herpes zoster. Herpes zoster is a disease which is characterized by a skin rash and is often associated with a lot of pain. Herpes zoster occurs in patients who have a normal or even a better antibody response in comparison to healthy subjects. So, it has been suggested that suppressed cellular immunity is implicated in the pathogenesis of herpes zoster. In previous studies it was shown that VZV-specific IFN-γ and TNF-α positive CD4 T lymphocytes are reduced in patients with SLE, and that in general, Treg (regulatory T) cells, NK (natural killer) and NKT (natural killer T) cells are also reduced in these patients in comparison to healthy controls. There was no significant difference in CD8 T cells in comparison to healthy subjects. In general, patients with RA showed an increase in CD4 T cells, specifically Th17 cells. The IL-17 production was also enhanced in patients with RA. However, like patients with SLE, patients with RA also showed a decrease in Treg cells. It depends on the given treatment whether a live-attenuated varicella vaccine might be an option for patients with SLE or RA. However, in most treatments it is probably not advisable to give a live-attenuated varicella vaccine to patients with SLE or RA, because there is a high risk that the vaccine will trigger the development of herpes zoster. This is because these patients have a suppressed cellular immunity. There are no studies yet that investigated if a herpes zoster vaccine can be used in patients with SLE or RA. So, future studies are necessary to know what level of immunosuppression makes patients at risk for infections caused by vaccination and to get a better understanding of the risks and benefits associated with varicella vaccination in patients with SLE or RA.
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Introduction

Primary infection with a Varicella Zoster virus (VZV) results in chickenpox. Chickenpox is an illness that is highly contagious. In temperate climates, the incidence of chickenpox is 13-16 cases per 1000 people per year. In these countries it is most common in children aged 1-9 years old. This is in contrast with tropical countries like India, where the incidence of chickenpox is higher in adults (1).

After primary infection, VZV reacts in around 15% of the general population (2). This reactivation usually occurs decades after primary infection. The reactivation of VZV leads to herpes zoster (2-14). The annual incidence of herpes zoster in the general population is less than 0,5% (6). Each year nearly 1 million people in the United States develop herpes zoster (9, 12, 15). Herpes zoster mostly occurs in older adults and immunosuppressed subjects (3, 6-8, 13, 16).

The most frequent complication in people with herpes zoster, is postherpetic neuralgia (14, 17). 8-27% of the individuals with herpes zoster will develop postherpetic neuralgia (17). Herpes zoster and postherpetic neuralgia are associated with severe pain and this can diminish the patient’s quality of life (9, 14, 16). Postherpetic neuralgia is also associated with impaired emotional well-being, decreased social function, poor sleep and difficulties with carrying out activities of daily life (12).

Another problem is that herpes zoster and postherpetic neuralgia have a negative impact on the productive work life of individuals. In a study by Drolet et al., it was shown that 64% of the 88 employed people reported to be absent from work and 76% reported a decreased effectiveness at work. This was due to herpes zoster and postherpetic neuralgia (17).

Before routine vaccination was introduced in the US in 1995, almost all children developed a primary varicella infection before the age of 15. In the majority of the world the varicella vaccine is still not routinely given, for example in countries like the UK, France, Australia, China and Japan (2). A varicella infection is normally benign, but in adults and immunocompromised individuals it can be life-threatening (1, 6). Especially people with an autoimmune disease are at high risk for developing herpes zoster. This is because most of the time these patients are receiving immunosuppressive therapies (3, 5, 6, 13, 15, 16).

Earlier research shows that a live-attenuated varicella zoster vaccine (Zostavax) was effective in preventing herpes zoster and postherpetic neuralgia in older people (≥60 years old) (3, 8, 9, 11, 16, 17). It also seems to be effective among individuals between 50-59 years old (11, 17). However, there are concerns about giving a live-attenuated varicella vaccine to people that are immunocompromised. The concern is that the vaccine could trigger the development of herpes zoster, instead of giving these patients immunity against VZV (3, 8, 18).

In this study we will investigate the immunity against VZV in people with an autoimmune disease. The focus will be on two autoimmune diseases, called systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). We will do this by investigating literature about the immunity against VZV in patients with SLE or RA. The purpose of this study is to see whether a live-attenuated varicella vaccine could be a possibility for patients with SLE or RA.
Varicella infection

VZV is an alpha virus, which belongs to the human herpesviruses (10, 16). The only known hosts for VZV are humans (1, 10, 16). VZV can disseminate from the nasopharynx via droplets and aerosols. It can also disseminate from skin lesions (1).

Varicella infections show seasonality in temperate and most tropical climates (1, 16). The peaks of this infection occur in the cooler months, during winter or spring. In temperate climates it has been reported that varicella infections occur every 2-5 years (1). In temperate countries, 90% of the population are exposed to chickenpox by the age of 16. This is lower in tropical countries (16).

Epidemiological factors that contribute to an outbreak of chickenpox are the ambient temperatures in the winter, and people who are living in close proximity in a naïve community. When people are living close to each other, there can be a rapid transmission of the virus (1).

When people are primarily infected, they will develop chickenpox (1, 10). The incubation period of VZV is usually 14-16 days. Chickenpox is characterized by a skin rash and is highly contagious (2). The contagious period starts 1-2 days before the rash is visible and lasts until all the vesicles are crusted. This is usually within 5-7 days (1).

Latent VZV can stay present in the sensory ganglia. As mentioned before, VZV can reactivate decades after primary infection and causes herpes zoster. Herpes zoster is characterized by a dermatomal, vesicular rash and is often associated with severe, unilateral pain (9-11). The rash of herpes zoster is attributed to the axonal transport of VZ virions to the skin. VZ virions are assembled in neuronal cell bodies. Neuronal cell bodies have to be infected in order for the virus to get access to the peripheral nerve axons, for transport to the skin.

Often there are also prolonged neurological signs and symptoms in people with herpes zoster (10).

In most people with herpes zoster, the rash and the associated acute pain will disappear within 1-2 months. However, in some patients the acute symptoms of herpes zoster can be followed by irreversible skin damage and sensory abnormalities. This results in a persistent pain that can be present for a long time. The pain can be a constant or an intermittent spontaneous pain. This is called postherpetic neuralgia (14).
Autoimmune diseases

Autoimmune diseases occur when the immune system attacks organs or tissue of the own body. Normally, the immune system is able to discriminate between self and non-self. However, when these mechanisms fail, it can lead to autoimmune diseases. Autoimmune diseases can be divided in two general categories: organ-specific varieties (for example type 1 diabetes) and non-organ-specific varieties (for example SLE and RA). In non-organ-specific varieties, the immune system attacks multiple organs and tissues (19). As mentioned before, the focus in this study will be on SLE and RA.

Systemic lupus erythematosus (SLE)

SLE is a chronic autoimmune inflammatory disease (20-24), in which dysfunction of the adaptive immune response causes attacks on several tissues and organs, including the skin, kidneys and the joints (21). SLE is characterized by episodic symptoms of widespread inflammation of blood vessels and connective tissues (25) and may cause severe organ impairment and even death (26). SLE often occurs in women between 20-40 years old (23). The prevalence is very high among African Americans, African Caribbeans, Hispanics and Asians (27). The cause of this disease is still unknown. A few probable risk factors are genetic predisposition, use of drugs and environmental factors (22, 24).

B cells play a central role in the pathogenesis of SLE. The main function of B cells is to produce antibodies. Normally this is for protecting the body against pathogens. However, in autoimmune diseases these antibodies attack self-antigens (20). Autoantibodies are a major diagnostic feature of SLE and are also important for monitoring SLE (23). Especially, the anti-dsDNA and anti-Sm antibodies are highly specific for SLE. These antibodies have a high diagnostic value (21).

A mark for SLE are antibodies that are directed against several cellular molecules and structures. Antibodies are secreted by B-cells and that is why SLE is considered a B-cell disease. In mouse models it is shown that SLE still occurs when the B cells are unable to secrete antibodies. So, this means that B cells may have an antibody-independent role in the pathogenesis of SLE. The B lymphocytes in mouse models have still an antigen presenting function and can produce cytokines, so maybe these functions play a role in the pathogenesis of SLE (20).

B lymphocyte stimulator (BlyS) protein (also known as BAFF) is a member of the tumour necrosis factor (TNF) ligand superfamily. BAFF pathways seems to be important in the development, survival and function of B cells. BAFF also seems to have a role in the pathogenesis of SLE. In several studies an increase in BAFF levels was found in patients with SLE or RA. SLE patients have an increased frequency of B cells and plasma cells, so therefore it has been supposed that BAFF might be a good therapeutical target (20).

It is suggested that T lymphocytes, NK cells and NKT cells also play an important role in the pathogenesis of SLE (21). It is also shown that SLE is characterized by interferon and complement activation. The elevation of interferon proteins and/or the activity of these proteins are associated with an up-regulation of interferon-inducible genes. This is also thought to have a contribution in the pathophysiology of SLE (23).
Patients with SLE are often treated with corticosteroids or immunosuppressive treatments. One of these treatments is called Belimumab. Belimumab is an example of an anti-human BAFF monoclonal antibody (20). Belimumab was the first biologic agent approved for treatment of SLE by the US Food and Drug Administration (FDA) (26, 28). Another biologic agent which can be used in patients with SLE is rituximab. This is an anti-CD20 monoclonal antibody, leading to temporarily depletion of B-cells (27, 29).

Other examples of treatments that can be used in patients with SLE are disease modifying anti-rheumatic drugs (DMARDs). Two examples of DMARDs that can be prescribed are methotrexate (MTX) and cyclophosphamide (10, 29).

Rheumatoid arthritis (RA)
RA is an autoimmune disease, which is characterized by chronic synovial inflammation (29-31). This can lead to cartilage and bone damage and eventually this can destruct the joints (31). The prevalence of RA in the general population is 0.5-1%. RA is more common in women and it affects people during their most productive years (32).

Before the clinical manifestations in RA occur there is a prodromal phase. This prearticular period is characterized by the presence of anti-citrullinated peptide/protein antibodies (ACPA), rheumatoid factor (RF) and lipid dysregulation. ACPA and RF are biomarkers of specific autoimmunity in people with RA and can be used for the early diagnosis of RA (29).

B lymphocytes are implicated in the pathogenesis of RA (30). As mentioned before, B lymphocytes produce antibodies which are for protecting the body against pathogens. However, in patients with RA these antibodies attack self-antigens (20). T lymphocytes are also implicated in the pathogenesis of RA. T-regulatory (Treg) cells for example have a critical role in the maintenance of peripheral immune tolerance and the prevention of chronic inflammation. A reduced number or a defective function of Treg cells has been described in many autoimmune disorders, including SLE and RA (31). Another component of the immune system which seem to play a role in the pathogenesis of RA are macrophages (33).

Patients with RA are generally treated with DMARDs (29, 34). The most commonly prescribed DMARDs are MTX, hydroxychloroquine (HCQ), sulfasalazine (SSZ) and leflunomide. The most frequently used drug worldwide in the treatment of RA is MTX. MTX can inhibit the proliferation of the inflammatory synovial cells (29).

Besides the DMARDs, there are also the more recently introduced biologic therapies. Biologic agents are currently being used earlier in the course of the disease in patients with poor prognostic factors. However, normally these agents are still reserved for patients with true DMARD failure (29). These biological agents include; TNF-α and IL-antagonists (infliximab, adalimumab, etanercept, anakinra), antibodies against B lymphocytes (rituximab), and inhibition of the T-cell co-stimulation (CTLA-4-Ig, called Abatacept) (31).
Immunity to VZV in patients with systemic lupus erythematosus

One of the most common causes of morbidity and mortality in patients with SLE are infections (4). Patients with SLE have a higher risk for developing herpes zoster, compared to healthy subjects (see figure 1) (4-6, 13, 15, 16, 18). A study by Borba et al. showed that there was no association between the incidence of herpes zoster and disease activity. In fact, the majority of herpes zoster incidences occurred during mild or inactive disease (4). In most cases these patients get corticosteroids, immunosuppressive treatments, or both (4-6, 13, 18). An earlier study showed that corticosteroids and/or immunosuppressive drugs were independent risk factors for infections in adults with SLE (4). These treatments may lead to a further reduction in the resistance to pathogens, like VZV (5, 6, 13, 18). A study by Nagasawa et al. showed that herpes zoster occurred in patients with SLE with an incidence of 43% and an annual incidence of 9% (13).

The suppression of the cellular immunity has been implicated in the pathogenesis of herpes zoster. This is because herpes zoster occurs in patients who are positive for antibodies (4-7, 9, 11, 13, 15, 16, 35). In a study by Nagasawa et al. for example, it was shown that antibody titres to VZV were equal or higher in patients with SLE in comparison to normal subjects (see figure 2) (13).

These findings suggest that patients with SLE may have a normal or even a better antibody response to VZV in comparison to normal subjects (13). Despite this good antibody response, the incidence of herpes zoster in patients with SLE remains high. From this we can conclude that antibodies will probably not prevent herpes zoster. So, the high incidence of herpes zoster in patients with SLE may be due to an impaired cellular immune response (13, 35). The cellular immunity has been supposed to be important for limiting the progression of varicella and for preventing herpes zoster (15).
The study by Nagasawa et al. also reported that patients with SLE had a significantly lower frequency of positive delayed skin reactions to the VZV antigen in comparison to healthy individuals. This suggests that patients with SLE have a decreased cellular immunity against VZV (35).

Abnormalities in T cell function are evident in SLE patients (4, 21). In particular, the total number of peripheral blood T cells is often reduced. The T cell activation properties are also defective in most patients with SLE (21).

In a study by Park et al. it was shown that patients with SLE had decreased VZV-specific memory CD4 T cell responses compared to healthy subjects and patients with RA. CD4 T cells are very important in the defense against viral infections. CD4 T cells can produce IFN-γ and TNF-α. IFN-γ and TNF-α are cytokines which can have direct inhibitory effects on the replication of VZV. They can also have immune modulating effects to enhance the expansion of effector T cells. Virus specific IFN-γ or TNF-α positive CD4 T cells can induce a persistent immunity to viral antigens, for example VZV (35).

Patients with SLE had a marked decrease in VZV-specific IFN-γ and TNF-α positive CD4 T cells, compared to healthy controls (see figure 3). There were no significant differences found among the groups in the case of CD8 T cells (not shown) (35).

![Figure 3. Distribution of individual values of VZV-specific IFN-γ (A) and TNF-α-positive (B) CD4 T cell frequencies in the three study groups (normal subjects, and patients with RA and SLE). Individual ratio values are plotted: horizontal bars indicate the mean ratio for each group. P values calculated by Student independent t-test (35).](image)

Treg cells are also reduced in patients with SLE (31), but this will be discussed in further detail in the chapter: immunity in people with rheumatoid arthritis.
Recently, it has been suggested that in general, natural killer (NK) cells and NKT cells also play a role in the pathogenesis of SLE. NK cells play an important role in both innate and adaptive immunity. Patients with SLE have low numbers of NK cells circulating in the blood and the NK cells have impaired cytotoxic properties in all stages of the disease activity (21). NKT cells share the properties of NK cells and T cells. NKT cells are also decreased in SLE patient, compared to healthy individuals. NKT cells can rapidly produce large amounts of cytokines, such as IFN-γ. As mentioned before, IFN-γ is also decreased in patients with SLE (see figure 2A) (21).

Glucocorticoid and immunodepressant agents are standard treatments for SLE (13, 21). In untreated patients with SLE a decrease in CD4 cells and normal or increased CD8 cells is often noted. Corticosteroid treatment preferentially decreases CD4 cells and so the CD4/CD8 ratio will be more decreased. This low ratio may explain the high incidence of herpes zoster in patients with SLE (13).

Cyclophosphamide is an immunodepressant and is known to influence the cell cycle and DNA synthesis. Four weeks of treatment with cyclophosphamide led to a significant increase in CD4 T cells (see figure 4). Cyclophosphamide treatment produced no significant change in B cells. After 4 weeks of cyclophosphamide treatment, only the NK cells remained significantly lower when compared to healthy controls (21).

Rituximab specifically depletes CD20 B cells (26, 29). Its main B-cell depleting activity involves antibody-dependent B-cell-related cytotoxicity (29). In a study by Teng et al. it was shown that rituximab significant reduces the absolute B-cell numbers in peripheral blood in patients with RA. There was also observed a significant increase in serum BAFF concentrations after the 1st rituximab treatment. After 24 months serum BAFF concentrations were significantly increased (34).
Immunity in people with rheumatoid arthritis

Patients with RA have a higher risk for developing herpes zoster, compared to healthy subjects (see figure 5)(3, 5, 7, 8, 15, 16, 18). The rate of herpes zoster in patients with RA is 2 to 5 times higher than the rate of herpes zoster in the general population (15). The disease itself is a risk factor, but patients with RA also get immunosuppressant. These patients require most of the time long-term immunosuppression, which leads to a further reduction in the resistance to VZV (3, 5, 7, 8, 13, 15, 18).

Figure 5. Risk of herpes zoster in patients with RA (5).

In general, plasma cells and B lymphocytes are a dominant component in the inflammatory response in RA. The RA synovial tissue is an ideal milieu for plasma cell differentiation, accumulation and persistence. Plasma cells in synovitis may contribute to joint damage by antibody production and by the secretion of proinflammatory factors. Especially, CD20+ and CD38– B cells with impaired proliferative responsiveness might play a role in the pathophysiology of RA. CD5+ B cells also seem to be expanded in non-organ-specific autoimmune diseases such as RA (33).

In addition to the B lymphocytes, T lymphocytes also play an important role in the pathogenesis of RA. A large proportion of the cells that infiltrate the synovium in RA patients, are T cells (33). In RA patients there is an accumulation of CD4+ T cells (22). Earlier research reported that Th17 cells (which belong to the CD4 T cells) are increased in patients with RA. Th17 cell-associated cytokines (like IL-17) are also significantly increased in plasma from RA patients, during the active phase (30).

Figure 6 shows that CD3+CD8 IL-17+ T cells, in peripheral blood mononuclear cells, were significantly higher than those in the control group. This was only in the active phase of the disease. There was no significant difference between the inactive phase of patients and the controls (30).
Figure 6. The CD3⁺CD8⁻IL-17⁺ cell ratio in RA patients. The results were shown as means ± SD. * P < 0.05 compared with the control group (30).

Another dominant component in the RA synovium are macrophages. Macrophages are responsible for the production of proinflammatory cytokines. They can secrete chemo-attractants and growth factors, which play an essential role in the chronicity of the inflammatory process (33).

As mentioned before, Treg lymphocytes are deficient in patients with different conditions, including SLE and RA. Treg cells can inhibit harmful immunopathological responses directed against self or foreign antigens. Treg cells express the receptor CTLA-4, which is a T cell inhibitory receptor. This receptor can inhibit T-cell activation by reducing IL-2 production and IL-2 expression. It also arrests T cells at the G1 phase of the cell cycle. CTLA-4 plays an important role in T-cell homeostasis and/or the development and activity of Treg cells. It has been reported that CTLA-4 expression by Treg cells is significantly reduced in RA patients, compared to healthy people (31).

Abatacept (CTLA-4-Ig) is one of the biological agents that is being given to patients with RA. CTLA-4 is approximately 70% homologous to CD28 and binds to the same ligands as CD28 (CD80 and CD86). The binding between CTLA-4-Ig and CD80/CD86 on antigen-presenting cells blocks the engagement of CD28 on T cells. So, its blocking the second signal (co-stimulation) which is necessary for the activation of effector T lymphocytes. Abatacept induces a decrease in the number of Treg cells, whereas it enhances the suppressive function of these lymphocytes. It has been suggested that abatacept reduces the number of Treg cells, because the CD28 signals may be important for the expansion and survival of Treg lymphocytes (31).

Other therapies with different biological agents (like rituximab or anti-TNF-α) has been reported to enhance the number of Treg cells and improve the function of these Treg cells (31). Rituximab can also inhibit the Th17 response (34).
Discussion

Patients with an autoimmune disease such as SLE or RA have a high risk for developing (severe) infections, like herpes zoster. It has been suggested that suppression of the cellular immunity has been implicated in the pathogenesis of herpes zoster (4, 5, 13, 15). This is because herpes zoster occurs in patients with a normal or even a better antibody response, compared to healthy subjects (13, 15).

Patients with SLE have decreased VZV-specific memory CD4 T cell responses in comparison to healthy controls, in particular virus specific IFN-γ- and TNF-α- positive CD4 T cells are reduced. Patients with SLE show no difference in CD8 T cells in comparison to healthy controls. Another type of T lymphocytes which are in general reduced in patients with SLE, are the Treg cells. Recent studies also suggest that in general, NK and NKT cells are reduced in patients with SLE and that NK cells showed impaired cytotoxic properties. Normally T lymphocytes, NK cells and NKT cells play an important role in killing pathogens, like VZV. The reduction of these cells in patients with SLE means that these patients have a higher risk for developing infections like herpes zoster.

In general, patients with RA show increased CD4 T cells, specifically Th17 cells. Th17 cell-associated cytokines (like IL-17) are also significantly increased in plasma from RA patients. Like patients with SLE, patients with RA also showed a decrease in Treg cells. Another major component in the immune responses in RA are macrophages. These cells all contribute to inflammatory responses in RA.

Vaccination with a live-attenuated varicella vaccine is probably not advisable in patients with SLE who are treated with corticosteroids or rituximab, or in patients with RA who are treated with abatacept. Corticosteroid treatment preferentially decreases CD4 T cells and rituximab is a monoclonal antibody which depletes specifically CD20 B cells. In patients with RA who are treated with abatacept, the activation of T lymphocytes is inhibited. T lymphocytes are very important in protecting the body against pathogens like VZV. A suppressed cellular immunity has been implicated in the pathogenesis of herpes zoster. So, in these patients there is probably a very high risk that a live-attenuated varicella vaccine would trigger the development of herpes zoster, instead of giving these patients immunity against VZV.

Rituximab has been reported to enhance the number of Treg cells and improve the function of these Treg cells in patients with RA, but it is also inhibiting the Th17 response in these patients. Treg cells can inhibit harmful immunopathological responses directed against self or foreign antigens. So, when these cells are enhanced, there is a greater inhibition of immunopathological responses against VZV. Th17 cells play an important role in killing pathogens, like VZV. A reduction in these cells will lead to a higher risk of developing herpes zoster. So, there may be a high probability in these patients that a live attenuated varicella vaccine will trigger the development of herpes zoster. This is why vaccination in these patients may be dangerous.

In patients with SLE who are treated with cyclophosphamide for 4 weeks, CD4 T cells are increased. Only the NK cells remained significantly lower with cyclophosphamide treatment, when compared to healthy controls. Maybe it is possible to give these patients a live-attenuated varicella vaccine, because there is no significant difference in CD4 T cell level in comparison to healthy subjects. However, it is not yet known whether this would be enough to prevent herpes zoster and give these patients immunity against VZV.
In 2008 the American College of Rheumatology (ACR) did not recommend the administration of a zoster vaccine to patients with RA or other rheumatic diseases (such as SLE) treated with biologics (3). The European league against rheumatism (EULAR) also recommended that live attenuated vaccines should be avoided whenever possible in immunosuppressed patients with autoimmune diseases like SLE and RA. It may be considered in mildly immunosuppressed patients, but this has to be done on a case-by-case basis (18).

A limitation of this study is that in the case of RA, we only found studies about the immune response in general. So, in these patients we did not find any studies about the immune response specifically against VZV.

In this study we did not include medication dose. There is a probability that this can be important for concluding whether a vaccination is a possibility in patients with SLE or RA.

Another limitation is that we only looked at a few immunosuppressive treatments. There are a lot of treatments that can be used in patients with SLE or RA. So, maybe there is a possibility for vaccination in patients with SLE or RA, when they are treated with other immunosuppressive therapies.

It may be considered to temporary discontinue the immunosuppressive medication before vaccination with a live attenuated virus. However, there are no studies yet that can support this strategy. It would also be highly advisable to offer vaccination to these patients before the treatment with biologicals or immunosuppressive treatments have started.

Another option which may be considered, is to give patients with an autoimmune disease an inactivated vaccine, instead of a live attenuated vaccine.

In conclusion: the results in this study have shown that a live-attenuated varicella vaccine in patients with SLE or RA is probably not advisable, because there is a high risk that the vaccine will trigger the development of herpes zoster. However, future studies are necessary to know what level of immunosuppression makes patients to be at risk for infections caused by the vaccination. There are no studies yet that investigated whether a herpes zoster vaccine can be used in patients with SLE or RA. So, future studies are also necessary for a better understanding of the risks and the benefits associated with varicella vaccination in patients with an autoimmune disease who are treated with immunosuppressive treatments.
References


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