Background document on

Immune-mediated inflammatory diseases (IMID)

Module 1

Vaccination in patients with autoimmune inflammatory rheumatic diseases (AIIRD)

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**Abbreviations**

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<tr>
<td>ACIP</td>
<td>Advisory Committee on Immunization Practices</td>
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<td>AIIRD</td>
<td>Autoimmune inflammatory rheumatic disease</td>
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<td>AS</td>
<td>Ankylosing spondylitis</td>
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<tr>
<td>BAG</td>
<td>Bundesamt für Gesundheit</td>
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<td>BD</td>
<td>Behçet's Disease</td>
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<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<td>CD</td>
<td>Cluster of Differentiation</td>
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<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CTD</td>
<td>Connective tissue disease</td>
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<tr>
<td>CTLA</td>
<td>Cytotoxic T-Lymphocyte Antigen</td>
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<tr>
<td>DMARD</td>
<td>Disease modifying anti-rheumatic drug</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
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<tr>
<td>MMR</td>
<td>Mumps, measles, rubella</td>
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<tr>
<td>MTX</td>
<td>Methotrexate</td>
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<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drug</td>
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<td>RA</td>
<td>Rheumatoid arthritis</td>
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<td>RR</td>
<td>Risk ratio</td>
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<td>RTX</td>
<td>Rituximab</td>
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<td>SGR</td>
<td>Schweizerische Gesellschaft für Rheumatologie</td>
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<tr>
<td>SLE</td>
<td>Systemic lupus erythematosus</td>
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<td>SpA</td>
<td>Spondylarthritis</td>
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<td>TNF</td>
<td>Tumor necrosis factor</td>
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<td>TT</td>
<td>Tetanus toxoid</td>
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<td>WG</td>
<td>Wegener's granulomatosis</td>
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<td>YF</td>
<td>Yellow fever</td>
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<td>PCV</td>
<td>Pneumococcal conjugate vaccine</td>
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<td>PPV</td>
<td>Pneumococcal polysaccharide vaccine</td>
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Search strategy

Published evidence was searched for in electronic databases (Cochrane, Medline, Pubmed, Embase). Unpublished (grey) literature (unpublished reports, conference abstracts) was retrieved through a targeted website search of relevant organizations and international conferences dealing with vaccination, infectious diseases and rheumatology. Additional articles were identified through reference lists of selected papers.

The following search terms were used in combination:


Mostly English and German articles were included. A summary of all relevant papers was produced. Data from meta-analyses, systematic reviews, randomized trials, and observational studies, but not case reports were taken into account, with the exception of one study of pneumococcal vaccine in patients with Behçet’s disease by Hugle et al. as this was considered to report important information.
General and selected specific aspects

- There are no specific contraindications for vaccination with inactivated and live vaccines in patients with autoimmune inflammatory rheumatic disease (AIIRD) without immunosuppressive treatment
- In general, vaccinations do not cause autoimmune inflammatory diseases, nor their exacerbations
- The vaccination status of the patients should be assessed at the earliest time point after the diagnosis of an autoimmune disease and recommended vaccinations should be administered as soon as possible. If possible, vaccinate before initiation of immunosuppressive therapy. Live attenuated vaccines should be given at least 4-6 weeks before initiation of immunosuppressive treatment
- In already treated AIIRD patients vaccines should ideally be administered when immunosuppressive therapy is at the lowest
- It is generally safe to administer inactivated vaccines to patients with AIIRD under immunosuppressive treatment; the immunogenicity may be reduced
- The administration of live vaccines to immunosuppressed patients bears the risk of replication of the attenuated microorganism and invasive infections. Live vaccines with a high potential of replication (e.g. yellow fever vaccine) should generally be avoided in patients with autoimmune inflammatory rheumatic disease under treatments with a systemic immunosuppressive effect
- Live vaccines with a low risk of replication (typhoid oral vaccine, varicella/herpes zoster vaccine) may be used with caution in selected patients under immunosuppressive therapy
- The immune response to a booster vaccine administered during immunosuppressive treatment is considered to be less affected than a primary vaccine dose
- Depending on the drug, different intervals after immunosuppressive treatment are advised
- General recommendations for basic vaccinations also apply to patients with AIIRD
- In general, vaccinations recommended for specific risk groups, such as influenza and pneumococcal vaccine, are also recommended for patients with AIIRD as they may require a more comprehensive protection. Vaccination against hepatitis B is encouraged in all AIIRD patients and vaccination against human papillomavirus (HPV) in female patients with systemic lupus erythematosus (SLE) aged 11-14 years (up to the age of 26 years). Herpes zoster vaccination will be recommended in AIIRD patients aged > 50 years when the vaccine will become available in Switzerland
- In a patient undergoing immunosuppressive therapy and in which immunity to towards mumps, measles, rubella, varicella is unknown, a specific serology should be performed. The same approach should be followed in a person under immunosuppressive therapy who intends to travel to a yellow fever endemic area and received the yellow fever vaccination in the past
- Serology after a completed primary course of vaccination should be performed if the respective serology is available
- If the immunocompromised person is not protected against measles and/or varicella and has contact with an infected person: consider immunoglobulins/antivirals
- As the immunocompromised person may not be protected against diseases despite previous vaccination (e.g. against mumps, measles, rubella, varicella, influenza, pertussis), insist on checking vaccinating status of household and other close contacts and vaccinate if indicated
- Always prefer conjugate vaccines over polysaccharide vaccines because they induce higher affinity antibody responses, longer lasting immune responses and memory responses
1 Increased risk of infection in patients with rheumatic diseases

Infections are a substantial cause of morbidity and mortality in persons with autoimmune inflammatory rheumatic diseases (AllIRD) (1). A retrospective cohort study showed that patients with rheumatoid arthritis (RA) had a 1.7 times higher risk of acquiring a confirmed infection compared to persons without RA (95% confidence interval (CI) 1.42-2.03). Similarly, the risk of an infection requiring hospitalisation was higher in RA compared to non-RA patients (risk ratio (RR) 1.83, 95% CI 1.52-2.21)(2). On the one hand, the infection risk is elevated due to the autoimmune disease itself (3–5). On the other hand, the higher risk of infection is caused by the use of immunosuppressive and immunomodulatory drugs. The risk of infection has been shown to depend on the immunosuppressive medication used (6,7). In comparison with other disease modifying anti-rheumatic drugs (DMARDs), cyclophosphamide and systemic glucocorticoids were associated with a higher risk of infection with a risk ratio of 3.26 (95% CI 2.28-4.67) and 2.56 (95% CI 2.29-2.85), respectively. The risk of infection seemed to be dose-dependent (6,7). The risk under tumor necrosis factor (TNF) blocking therapy was even higher than under methotrexate (MTX) therapy or other non-biological treatments (8–10).

This was confirmed in a meta-analysis: anti-TNF-therapy appeared to increase the risk of infection compared to non-biologic agents (adjusted pooled risk ratio 1.37, 95%CI 1.18-1.60) (11). The risk of infection was especially increased under treatment with monoclonal antibodies (infliximab, adalimumab) (12). Among RA patients treated with biologicals, the risk of hospitalised infection was higher in infliximab treated patients compared to etanercept, adalimumab, abatacept or rituximab treated patients (13). A meta-analysis showed no increased risk of serious infections in RA patients treated with rituximab (RTX) or abatacept, compared to those treated with anakinra (14). The risk of infection appears to especially high in patients treated with anakinra (odds ratio (OR) 4.05 (95%CI 1.22-16.84) and those treated with certolizumab (OR 4.75, 95%CI 1.52-18.45) (15). In patients with systemic lupus erythematosus (SLE), infections were found to be one of the most common causes of death (28.9%) during the initial 5 years (16). In systemic sclerosis patients in Thailand, 13/31 deaths (42%) were associated with infections (17).

References


2 Risk of vaccine-preventable infections in patients with rheumatic diseases

2.1 Infections endemic in Switzerland

It was shown that elderly patients with rheumatic diseases and other chronic conditions have an increased risk for influenza infection, pneumonia and death (18–21). Similarly, the risk of pneumococcal pneumonia was shown to be elevated in patients with rheumatic diseases (22). Primary varicella infection can be severe and potentially fatal in immunocompromised persons (23–25). The risk for herpes zoster (HZ) is also elevated in RA and SLE patients compared to the general population (26–29). Therapy with TNF Alpha blocking agents may increase the risk compared to therapy with non-biologic agents (30,31). Looking at human papillomavirus (HPV), not only the risk of infection (32,33), but also the incidence of high-risk infection, multiple infections and cervical dysplasia (33,34) is increased in SLE patients; while clearance of the virus is decreased (34) compared to the general population. In immunocompromised persons, hepatitis B reactivation can be severe and can sometimes have a high mortality (35).

2.2 Infections endemic in other countries

Additionally, AIIRD patients are increasingly exposed to infections which are not endemic in Switzerland. International travel has substantially increased and reached one billion at the end of 2012 (36). In 2010 alone, 10 million international trips were undertaken by the Swiss population (37).

Several of the travel-associated diseases are vaccine preventable, such as: hepatitis A, poliomyelitis, japanese encephalitis, meningococcal meningitis, rabies, typhoid fever, yellow fever and cholera. So far, no data exist on the risk of acquiring these diseases in AIIRD patients, but it can be assumed that immunocompromised persons are at higher risk of acquiring any of these infections and that the infection will be more severe than in healthy individuals. In travellers treated with immunosuppressive agents, or in patients with inflammatory bowel disease, skin infections were found more often than in healthy controls (38). In a Dutch study, travellers with medical conditions had a higher risk of obtaining travel related diseases compared to healthy travellers, predominantly gastrointestinal in nature (39).

Tuberculosis: In RA patients, the tuberculosis risk has been shown to be increased 2.0 fold to 10.0 fold in comparison to the general population (40–42). The risk is especially increased in RA patients treated with TNF blockers (42). Treatment with the monoclonal TNF blocker infliximab increased the risk even further compared to the soluble TNF blocker (etanercept) (40). In Hong Kong and Korea, the TB incidence has been found to be higher in SLE patients than in the general population (43,44). One study found higher TB rates in SLE patients and a higher incidence of extra-pulmonary TB cases compared to RA patients (44).

References


3 Vaccinations and autoimmune diseases

There are specific situations whereby autoimmune reactions have been found to be related to vaccination. For the following situations an association between vaccination and onset of an autoimmune disease have been shown:

1. **Guillain Barré syndrome (GBS)** after 1976 swine influenza A (H1N1) subtype A/NJ/76 vaccination in the United States (45,46). The attributable risk of vaccine-related GBS was estimated to be around 1 case per 100’000 vaccinated adults.

   An increased risk of GBS after influenza A (H1N1) 2009 monovalent vaccination has been widely discussed and cannot be completely ruled out (47–59). A case-control study in 5 European countries could not demonstrate an increased risk of GBS after 2009 A (H1N1) influenza vaccination when taking influenza-like illness/upper respiratory infections and seasonal influenza vaccination into account (48). Obtaining data from six adverse event monitoring systems in the USA, a modest risk of GBS attributable to 2009 A (H1N1) influenza vaccination was found. With around 1.6 excess cases per 1’000’000 million vaccinated people the attributable risk has been estimated to be much lower than during the 1976 swine influenza A vaccination campaign (47).

2. It has been shown that mumps/measles/rubella vaccine can be associated with immune thrombocytopenic purpura (ITP) with around 1 case per 22'300-50'000 administered vaccine doses (60–64). A second MMR dose was not associated with an increased risk of ITP (65).

3. An increased risk for Guillain Barré syndrome could also be demonstrated for recipients of brain-derived rabies vaccine, which is not in use in Europe (66–68).

Also for different vaccine adjuvants an association with autoimmune diseases has been discussed, but an association could not be demonstrated (69–71).

**Conclusion:** These are the few antigen specific situations where an autoimmune reaction was found to be associated with vaccination.

**References**


50. Greene SK, Rett M, Weintrab ES, Li L, Yin R, Amato AA, et al. Risk of confirmed Guillain-Barre syndrome following receipt of monovalent inactivated influenza A (H1N1) and seasonal influenza vaccines in the Vaccine Safety Datalink


71. CDC - Veterans Health - Gulf War Studies - Defining Gulf War Illness. [cited 2013 May 21]; Available from: http://www.cdc.gov/nceh/veterans/default2g.htm
4 Infections and autoimmune diseases

The risk of autoimmune diseases can be greatly increased after an infection (72).

1. For example, the risk of GBS within 90 days after influenzalike illness was found to be 7 fold increased (Risk ratio 7.35, 95%CI 4.36-12.38) (57), and the risk of GBS after influenza infection is 4-7 times higher than after influenza vaccination (73).

It has also been shown that the risk of developing GBS is 77-100 times higher after a Campylobacter jejuni infection compared to the background rate in the general population (74,75).

2. An association between group A β-hemolytic streptococcal infection and rheumatic fever has also been clearly demonstrated (76).

3. Another example of an immune-mediated post infectious complication is poststreptococcal acute glomerulonephritis (77).

4. Common viral infections with e.g. adenovirus, parvovirus B19, herpes viruses, human enteroviruses, cytomegalovirus and also HIV and hepatitis C infections can be associated with the development of myocarditis (78).

5. It is also well known that acute thrombocytopenia can be associated with preceding viral illnesses, such as measles or varicella (79).

Conclusion: There is strong evidence for the role of infections in the development of several autoimmune conditions.

References


5 Safety and immunogenicity of vaccinations in AIIRD patients

There are several case reports of flare-ups of the underlying disease after vaccination and there has been a lot of debate about this topic (80). However, the majority of published data supports the conclusion that immunisation with inactivated vaccines is safe and does not increase disease activity in AIIRD patients, neither by clinical, nor by laboratory parameters (81–83).

5.1 Rheumatoid arthritis

5.1.1 Seasonal Influenza vaccine

Seasonal influenza vaccination was shown to be safe in patients with rheumatoid arthritis without medication and under treatment with corticosteroids, non-biological DMARDs, and non-biological DMARDs, including monoclonal and soluble TNFα blockers, the IL-6 blocker tozilizumab and the anti-CD20 antibody rituximab (RTX).

Immunogenicity was demonstrated under treatment with corticosteroids, non-biologic DMARDs, both monoclonal and soluble TNFα blockers and under tozilizumab treatment (84–96). In several studies, the immune response was reduced under MTX treatment (97), but still satisfactory (92,93). Also under treatment with infliximab, a reduced, but still satisfactory, immunogenicity could be observed in several studies (89,96). In one study, the timing of influenza vaccination in relation to infliximab influenced the immunogenicity of the vaccine (88). The antibody response was reduced when the vaccination was administered 3 weeks after the infliximab infusion, but it was not reduced when the vaccine was given on the same day as the infusion.

Also under rituximab treatment, the timing of vaccination in relation to RTX treatment was shown to be important. When influenza vaccination was administered 84 days after RTX treatment, the immune response was blunted (98). It was shown that B cells were completely depleted from day 28 to day 84 after RTX infusion (98). The humoral immune response was found to be partly restored when the influenza vaccine was administered 6-10 months after RTX treatment (99). In another study, influenza vaccination was less, but still sufficiently, immunogenic in patients under RTX treatment (90). But the time point of RTX treatment in relation to vaccination is not exactly reported.

Conclusion: Influenza vaccination can be safely administered in patients with rheumatoid arthritis. It is sufficiently immunogenic under immunosuppressive treatment, under corticosteroids, non-biological and biological DMARDs. MTX may have a negative effect on humoral immune responses. Under B-cell depleting therapy (rituximab), immune responses are probably insufficient when vaccine is administered within 1-3 months after RTX. Also inactivated vaccinations should be given before initiation of therapy, or 6-8 months afterwards.

Insist on checking the vaccination status of household and other close contacts. If they have not received the current seasonal influenza vaccine encourage them to be vaccinated.

References


5.1.2 H1N1 vaccine

Compared to other vaccinations, there are more data on the pandemic flu vaccine of the year 2009. Safety of H1N1 vaccination was demonstrated in patients with rheumatoid arthritis (RA) under treatment with corticosteroids, non-biological DMARDs, TNFα blockers, the CTLA-4 antagonist abatacept, the IL-6 blocker tozilizumab and the anti-CD20 antibody rituximab (100–105).

Immunogenicity was generally reduced under treatment with corticosteroids, non-biological DMARDs, TNFα blockers, abatacept and tozilizumab (100–105). In some studies, under TNF blocking therapy, the Committee for Medicinal Products for Human Use (CHMP) criteria for seroconversion (>40%), seroprotection and GMT ratio increases (>2.5) could be fulfilled (101,105). In other studies, immune responses were reduced under treatment with infliximab, adalimumab or etanercept (102). A negative effect of treatment with MTX (100,101,104,105), leflunomide and immunosuppressive drugs (azathioprin/mycophenolate mofetil/cyclophosphamide) (101), abatacept and rituximab could also be observed (100). The immunogenicity was especially reduced when the vaccination was administered after recent rituximab treatment (<12 weeks) (101). In one study by Ribeiro et al., abatacept was shown to reduce the humoral immune response even further compared to MTX (106). It could be shown that with a second vaccine dose, administered 3-4 weeks after the first dose, similar antibody titers and seroprotection rates (>=70%) could be achieved in patients compared to those in controls despite the inhibitory effect of several non-biological and biological DMARDs (incl. B-cell depletion) (101). In another study, a booster vaccination could produce seroprotection in 33% of those RA patients that did not respond to a first A/H1N1 vaccine (102).

**Conclusion**: H1N1 vaccination can be safely administered in patients with RA. Immunogenicity may be reduced under therapy with biological and non-biological agents. A booster dose 3-4 weeks after the first dose may be considered for new influenza strains or patients that have not been vaccinated against influenza before. Under B-cell depleting therapy (rituximab), immune responses are probably insufficient when vaccine is administered within 3 months after RTX. If possible, H1N1 vaccination should be given before initiation of therapy, or 6-8 months afterwards. Abatacept seems to severely reduce humoral immune response to H1N1 vaccination.

**References**


5.1.3 Pneumococcal vaccine

Pneumococcal polysaccharide (PPV) and conjugate vaccines (PCV) were safe in patients with RA (91,107,108).

Immunogenicity of PPV (91,109–111) and PCV (112,113) was generally good in RA patients treated with glucocorticoids or TNFα blockers. In one study, the immunogenicity of PPV was reduced under TNF blocking therapy (114).

In most studies, MTX treatment was associated with a lower immune response to both PPV (97,110,111,113) and PCV(112,113). In one prospective controlled study, no negative effect of MTX on the humoral immune response towards PPV was detected (109). A combination therapy of MTX + TNF hampered the immune response to PPV compared to MTX or TNF alone (115). Furthermore, the combination of RTX + MTX hampered the immune response to PPV (107), when the vaccine was administered 26 weeks after RTX treatment.

Immune responses to PPV were reduced in healthy subjects under abatacept therapy. The effect was strongest in those subjects who were vaccinated 2 weeks after abatacept treatment. In those who were vaccinated before the administration of abatacept the effect was minor (116). In one study, RA patients were vaccinated with PPV under abatacept treatment. Only 10/21 (48%) showed an immune response to ≥ 3 serotypes (117).

In one study, heptavalent PCV and PPV elicited similar antibody responses (113). Tozilizumab was shown to have no negative effect on humoral immune responses to PPV (80).

**Conclusion:** PPV and PCV can be safely administered in patients with RA. Immunogenicity may be reduced under therapy with MTX or under combination therapy with MTX and TNF blocker, or MTX and RTX. Under B-cell depleting therapy (rituximab), immune responses are probably insufficient when vaccine is administered within 3 months after RTX. Pneumococcal vaccination should be given before initiation of therapy, or 6-8 months afterwards. Pneumococcal vaccination should be given before abatacept treatment.

The PCV should be preferred over PPV as conjugate vaccinations produce higher affinity antibody responses, longer lasting immune responses, and the production of memory B cells. Booster vaccinations after conjugate vaccinations are possible while in polysaccharide vaccines secondary vaccines may elicit only poor immune responses due to a lack of memory cells. The administration of a first dose of plain polysaccharide vaccine may blunt the immune response to subsequent doses, such that the antibody levels following a second vaccination, and possibly the magnitude of clinical protection, may be lower than following a first vaccination.

**References**


5.1.4 Tetanus toxoid vaccine

Tetanus toxoid vaccination was shown to be safe in RA patients (86,107).

One study showed that tetanus toxoid vaccination was immunogenic in RA patients without immunosuppressive treatment (119). In another study, the immunogenicity was shown to be reduced, but the treatment with corticosteroids, azathioprine or chlorambucil did not have a negative effect (86).

Antibody responses to tetanus toxoid vaccination (i.e. a ≥ 4-fold rise in antibodies) were similar in those patients treated with RTX plus MTX or with MTX alone (39.1% vs. 42.3%), when administered 22 weeks after B-cell depleting therapy (107). That means, RTX treatment in addition to MTX did not have a negative effect on the immune response to the T cell dependent tetanus toxoid vaccine, when the vaccine was administered 24 weeks after RTX treatment.

Immune responses to tetanus vaccine were reduced in healthy subjects under abatacept therapy. The effect was strongest in those subjects who were vaccinated 2 weeks after abatacept treatment. In those who were vaccinated before the administration of abatacept the effect was minor (116).

**Conclusion:** Tetanus toxoid vaccine can be safely administered in patients with rheumatoid arthritis. Immunogenicity may be low under therapy with MTX. In MTX treated patients the immunogenicity was not further reduced by rituximab in one study. As immune responses may be insufficient when a vaccine is administered within 1-3 months after RTX it should be given before initiation of therapy, or 6-8 months afterwards. Tetanus vaccination should be given before abatacept treatment.

References


5.1.5 Hepatitis B vaccine

A course of three hepatitis B vaccinations (Engerix) could be safely administered to RA patients (120). After hepatitis B vaccination, only 15/22 (68%) of RA patients responded with antibody levels > 10 IU/l after 7 months. Patients were under treatment with corticosteroids, hydroxychloroquine, MTX, azathioprine, gold and/or sulfasalazine (120).

**Conclusion:** Hepatitis B vaccination can be safely administered to RA patients. As there are insufficient data on the immunogenicity of hepatitis B vaccination in RA patients, a serology should be performed 4-6 weeks after vaccination in immunosuppressed RA patients and, if necessary, further doses should be administered.

**Reference**

5.1.6 Hepatitis A vaccine

Hepatitis A vaccination was safe in patients with juvenile idiopathic arthritis (121).

The immunogenicity of hepatitis A vaccination was studied in 56 immunocompromised travellers, out of which 36% had rheumatoid arthritis. 43% of all patients under methotrexate, 28% of those under corticosteroid therapy and 20% of the patients under TNF blocking therapy, as well as both patients treated with tacrolimus did not develop sufficient hepatitis A antibodies (122).

The immunogenicity of hepatitis A vaccine was also studied in patients with juvenile idiopathic arthritis (121). 43/47 (91.5%) of the patients had a positive titer 2 months after 2 vaccines administered at a 6 months interval, while 67/67 (100%) of healthy controls developed a positive titer, P=0.027. The four patients with negative titers were treated with a TNFα blocker, and the other patients were treated with MTX, Prednisolone and/or salazopyrine.

**Conclusion:** Hepatitis A vaccination can be safely administered to RA patients. As there are insufficient data on the immunogenicity of hepatitis A vaccination in RA patients, a serology should be performed 4-6 weeks after vaccination in immunosuppressed RA patients.

If short term protection is necessary, a serology can be performed 4-6 weeks after the first dose and if necessary a second dose can be administered at a short interval.

For long-term protection, a serology should be performed 4-6 weeks after the regular second dose (dose 6 months after the first dose) and if necessary further vaccine doses should be administered.

**References**


5.1.7 Mumps, measles and rubella vaccine

The re-vaccination with mumps, measles, rubella (MMR) vaccine was safe in 207 patients with juvenile idiopathic arthritis (JIA). Out of these 49 were treated with MTX, 6 with other non-biological DMARDs and 1 with a TNF blocking agent (123).

The re-vaccination with MMR vaccine was shown to be safe and immunogenic in 15 patients with juvenile idiopathic arthritis under treatment with low-dose MTX. In some patients the soluble TNF blocker etanercept was given as concomitant treatment (124).

Re-vaccination with MMR was safe and immunogenic in 63 JIA patients compared to 68 JIA patients who did not receive a vaccination. Out of these, 9 patients were treated with biologicals (6: TNF antagonists (etanercept), 3: Interleukin 1 receptor antagonist (anakinra)) and the biological treatment was discontinued at 5 times their half-lives prior to vaccination. The other vaccinated patients were treated with classic DMARDs (29: MTX, dosage, median 10.6 mg/m²/week, IQR 9.7-11.2, 1: leflunomide, 2: oral glucocorticoids) (125).

Conclusion: Due to a lack of data and the theoretical risk of an infection through administration of an actively replicating live vaccine in patients under immunosuppressive therapy, primary MMR vaccination is contraindicated under high-dose corticosteroid therapy, therapy with non-biological or biological DMARDs.

Check the vaccination status /immune status before starting the immunosuppressive therapy. If 2 vaccinations in the past can be identified: start of treatment is possible. If there is no vaccination or only one vaccination in the past: vaccinate before initiation of therapy if possible. A live vaccine should be administered 3-4 weeks before initiation of therapy. Otherwise it is advisable to wait for at least 4 weeks after discontinuation of high-dose corticosteroid therapy, wait, in general, for at least 3 months after discontinuation of non-biological DMARD, and at least 3 months after discontinuation of a biological agent (see section 5).

Insist on checking the vaccination status of household and other close contacts, and vaccinate them if indicated.

If a seronegative person under immunosuppressive therapy was in contact with a person with varicella and/or measles infection, consider the administration of antivirals/immunoglobulins.

References


5.1.8 Varicella vaccine

A primary varicella vaccination was safe in 20 patients with juvenile rheumatic diseases who had a negative varicella titer before vaccination. All were under treatment with MTX (12-25mg/m2/day), 13 received prednisone additionally (2-20mg/day), and 5 other DMARDs (ciclosporine A, leflunomide, D-penicillamin). The immunogenicity was reduced. After one vaccination, 10 out of 20 (50%) of the patients with juvenile rheumatic diseases developed a positive titer, while 13 out of 18 healthy controls (72.2%) developed a humoral immune response (126).

**Conclusion:** Due to a lack of data and the theoretical risk of an infection through administration of a live vaccine in patients under immunosuppressive therapy, primary varicella vaccination is generally contraindicated under high-dose corticosteroid therapy, therapy with non-biological or biological DMARDs.

Check the vaccination status /immune status before starting the immunosuppressive therapy. If 2 vaccinations in the past can be identified: start of treatment is possible. If there is no vaccination or only one vaccination in the past, perform antibody surrogate test. If the surrogate marker is below the threshold considered protective: vaccinate before initiation of therapy if possible. A live vaccine should be administered 3-4 weeks before initiation of therapy. Otherwise it is advisable to wait for at least 4 weeks after discontinuation of high-dose corticosteroid therapy, wait, in general, for at least 3 months after discontinuation of non-biological DMARD, and at least 3 months after discontinuation of a biological agent (see section 5).

Insist on checking the vaccination status of household and other close contacts, and vaccinate them if indicated.

If a seronegative person under immunosuppressive therapy is in contact with a person with varicella and/ or measles infection, consider the administration of antivirals/immunoglobulins.

**Reference**

5.1.9 Herpes zoster vaccine

Out of 463'541 medicare beneficiaries (292'169 with RA, 89'565 psoriasis, 4'026 ankylosing spondylitis, 66'751 inflammatory bowel disease) 18'683 (4%) received the HZ vaccine. Patients were treated with TNF-α inhibitors, non-TNF-α biologic drugs, DMARDs and/or corticosteroids. A retrospective analysis showed that the receipt of HZ vaccine was not associated with an increase of HZ infections up to 42 days after vaccination. In the long-term (2 years of follow-up) the vaccination was associated with a protective effect (127).

The Advisory Committee on Immunization Practices (ACIP) states that “short-term corticosteroid therapy (<14 days); low-to-moderate dose (<20 mg/day of prednisone or equivalent); topical (e.g., nasal, skin, inhaled); intra-articular, bursal, or tendon injections; or long-term alternate-day treatment with low to moderate doses of short-acting systemic corticosteroids are not considered to be sufficiently immunosuppressive to cause concerns for vaccine safety. Persons receiving this dose or schedule can receive zoster vaccine. Therapy with low-doses of methotrexate (<0.4 mg/Kg/week), azathioprine (<3.0 mg/Kg/day), or 6-mercaptopurine (<1.5 mg/Kg/day) for treatment of rheumatoid arthritis, psoriasis, polymyositis, sarcoidosis, inflammatory bowel disease, and other conditions are also not considered sufficiently immunosuppressive to create vaccine safety concerns and are not contraindications for administration of zoster vaccine” (128).

Conclusion: At the moment Herpes zoster vaccine is not available in Switzerland. If it is available in the future ACIP recommendations may be followed.

References


5.1.10  Yellow Fever vaccine

Re-vaccination against yellow fever (YF) was safe in 70 patients with rheumatic diseases (54 of these with RA) under therapy with MTX, corticosteroids, sulfasalazine, leflunomide, cyclophosphamide and biological agents (129).

Re-vaccination against yellow fever was also safe in 17 patients with RA under treatment with infliximab, and partly under concomitant treatment with 15-20mg MTX/week (130). Vaccination against YF induced more moderate/severe local adverse events in 34 patients treated with low dose (≤20mg prednisone equivalent) or short-term (<15 days) corticosteroid therapy than in patients without corticosteroid therapy (12% vs. 2%) (131).

In patients under low-dose or short-term corticosteroid therapy, YF vaccination all patients reached neutralization titers of ≥ 1.10. 11/20 (55%) had been vaccinated against YF before. Immunogenicity did not differ between first-time vaccinees and those who had received YF vaccination before. When YF vaccine was administered 1 month after the infliximab infusion it was shown that YF re-vaccination tended to be less immunogenic in RA patients compared to healthy controls (130).

Conclusion: Due to a lack of data and the theoretical risk of an infection through administration of an actively replicating live vaccine in patients under immunosuppressive therapy, YF vaccination (primary and revaccination) is contraindicated under high-dose corticosteroid therapy, therapy with non-biological or biological DMARDs.

Check travel plans before starting the immunosuppressive therapy. If the indication for YF vaccination is given and if the subject consents to potential risks of the vaccine, a live vaccine should be administered 3-4 weeks before initiation of therapy. Alternatively, it is advisable to wait for at least 4 weeks after discontinuation of high-dose corticosteroid therapy, wait, in general, for at least 3 months after discontinuation of non-biological DMARD, and at least 3 months after discontinuation of a biological agent before administration of YF vaccination (see section 5). Discourage from travelling to a YF endemic country if vaccination is not possible.

References


In patients with rheumatoid arthritis, there are no published data on vaccinations against: polio, diphtheria, *Haemophilus influenzae* b, human papillomavirus, tick-borne encephalitis, rabies, meningococcal vaccine (polysaccharide or conjugate), japanese encephalitis (inactivated), typhoid fever (parenteral), typhoid fever (oral), cholera.
5.2 Connective tissue diseases

5.2.1 Seasonal Influenza vaccine

Seasonal influenza vaccine was demonstrated to be safe in patients with systemic lupus erythematosus under treatment with corticosteroids, non-biological DMARDs and TNF blocking agents (85,132–137). Safety of influenza vaccine was also demonstrated in patients with systemic sclerosis (137–139).

Immunogenicity of influenza vaccine in SLE patients under corticosteroid treatment was demonstrated in 2 studies (85,135). Another study showed a reduced immunogenicity under corticosteroid treatment (140). Immunogenicity could be demonstrated under treatment with non-biological DMARDs (85,135), azathioprine was shown to have a negative effect on the immune response in one study (136). Immunogenicity could be shown under TNF blocking therapy (85).

Conclusion: Influenza vaccination can be safely administered in patients with connective tissue diseases. It is sufficiently immunogenic under immunosuppressive treatment, under corticosteroids, non-biological and TNF Alpha blocking therapy. Under B-cell depleting therapy (rituximab), immune responses are probably insufficient when vaccine is administered within 1-3 months after RTX. Also inactivated vaccinations should be given before initiation of therapy, or 6-8 months afterwards.

Insist on checking the vaccination status of household and other close contacts. If they have not received the current seasonal influenza vaccine encourage them to be vaccinated.

References


5.2.2 H1N1 vaccine

H1N1 vaccination could be safely administered to patients with connective tissue diseases (CTD) (100,101,103,141–143).

H1N1 vaccination was shown to be immunogenic in CTD patients without treatment or under corticosteroids (100). Reduced immunogenicity was demonstrated in several studies (101,103). Seroconversion, seroprotection and GMT fold increases after vaccination were also lower in another study, but it could be shown that for seroconversion and GMT fold increase international immunogenicity criteria were met (142).

Reasonable immunogenicity could also be demonstrated under treatment with non-biological DMARDs and biologicals (138). Reduced immunogenicity in SLE patients treated with non-biological or biological DMARDs was reported in 5 studies (100,101,103,142,143). One study demonstrated good immunogenicity under chloroquine monotherapy or combination treatment (142). In two studies, a second H1N1 vaccination enhanced antibody titers and seroprotection rates in patients to a similar as in healthy controls (101,143).

Methotrexate, recent rituximab therapy (<12 weeks) and abatacept treatment had a negative effect on humoral immune responses (100).

**Conclusion:** H1N1 vaccination can be safely administered to patients with connective tissue diseases. Immunogenicity may be reduced under corticosteroids, non-biological and biological treatment.

Under B-cell depleting therapy (rituximab), immune responses are probably insufficient when vaccine is administered within 3 months after RTX. Also inactivated vaccinations should be given before initiation of therapy, or 6-8 months afterwards.

If possible, influenza vaccination against new influenza strains vaccination should be given before abatacept treatment.

For new influenza strains and individuals that have not been vaccinated against influenza before two vaccinations should be considered.

**References**


5.2.3 Pneumococcal polysaccharide vaccine (no data on conjugate vaccine)

Pneumococcal polysaccharide vaccine could be safely administered in patients with connective tissue diseases (109,144–147).

Immunogenicity could be demonstrated in patients with systemic sclerosis. These patients were under treatment with cyclophosphamide, low dose corticosteroids, colchicine and/or D-penicillamine (148). Immunogenicity could also be demonstrated for patients with systemic lupus erythematosus, even under corticosteroid and/or cyclophosphamide/azathioprine therapy (149).

Reduced, but sufficient, immunogenicity of PPV could be demonstrated in 3 studies for CTD patients under treatment with corticosteroids and non-biological DMARDs (107,141,145). Humoral immunity to pneumococcal vaccine seemed to diminish more rapidly than in healthy controls (150).

Immune responses to PPV were reduced in healthy subjects under abatacept, especially when vaccinated 2 weeks after abatacept treatment (116).

**Conclusion:** PPV can be safely administered in patients with connective tissue diseases. In general, immunogenicity after vaccination is satisfactory. But data on patients under TNF blocking therapy are missing. Under B-cell depleting therapy (rituximab), immune responses are probably insufficient when vaccine is administered within 1-3 months after RTX. Pneumococcal vaccination should be given before initiation of therapy, or 6-8 months afterwards. Pneumococcal vaccination should be given before abatacept treatment.

The conjugate vaccine should be preferred over polysaccharide vaccinations as conjugate vaccinations produce higher affinity antibody responses, longer lasting immune responses, and the production of memory B cells. Booster vaccinations after conjugate vaccinations are possible while in polysaccharide vaccines secondary vaccines may elicit only poor immune responses due to a lack of memory cells. The administration of a first dose of plain polysaccharide vaccine may blunt the immune response to subsequent doses, such that the antibody levels following a second vaccination, and possibly the magnitude of clinical protection, may be lower than following a first vaccination.

**References**


5.2.4 Tetanus toxoid vaccine

Tetanus toxoid vaccine could be safely administered in patients with systemic lupus erythematosus (145).

In one study, immunogenicity of tetanus toxoid vaccination in 24 patients with SLE without immunosuppressive treatment could be demonstrated (119), while in another study in 9 patients without immunosuppressive treatment, immune responses were diminished (151).

In another study, the overwhelming majority of SLE patients developed protective antibodies after immunization. But there was a trend towards lower antibody increases when patients were treated with prednisone, cyclophosphamide, or azathioprine (145).

Immune responses to tetanus vaccine were reduced in healthy subjects under abatacept therapy. The effect was strongest in those subjects who were vaccinated 2 weeks after abatacept treatment. In those who were vaccinated before the administration of abatacept the effect was minor (116).

**Conclusion:** Tetanus toxoid vaccine can be safely administered in patients with connective tissue diseases. Immunogenicity may be lower in patients with connective tissue diseases than in the healthy population. Immune responses may be insufficient when vaccine is administered within 1-3 months after RTX. It should be given before initiation of therapy, or 6-8 months afterwards. Tetanus vaccination should be given before abatacept treatment.

**References**


5.2.5 Hepatitis B vaccine

Hepatitis B vaccination could be safely administered to 28 SLE patients with quiescent disease (152). Hepatitis B vaccination induced adequate humoral immune responses in SLE patients with inactive disease. 2/28 (7%) patients did not seroconvert after the 3rd dose and received another dose. After the fourth dose, positive anti-HBs were detected. None of the patients received immnosuppressive treatments or glucocorticoids > 20mg/day (152).

**Conclusion:** Hepatitis B vaccination can be safely administered to SLE patients. As there are insufficient data on the immunogenicity of hepatitis B vaccination in SLE patients under immunosuppressive treatments, a serology should be performed 4-6 weeks after vaccination in immunosuppressed SLE patients and, if necessary, further doses should be administered.

**Reference**

5.2.6  *Haemophilus influenzae* b vaccine

Safety was demonstrated in SLE patients (145).

The overwhelming majority of SLE patients developed protective antibodies after immunization. There was a trend towards lower antibody increases when patients were treated with prednisone, cyclophosphamide, or azathioprine (145).

**Conclusion:** Consider vaccination in case of epidemiological or personal risk.

**Reference**

5.2.7 Human Papilloma Virus vaccine

The human papillomavirus (HPV) vaccine against serotype 6,11, 16, 18 (Gardasil) was shown to be safe in 50 SLE patients with stable disease (153).

The quadrivalent HPV vaccine was reasonably effective in SLE patients with stable disease (153).

**Conclusion:** SLE patients have a higher HPV risk than the general population, especially high-risk infections and multiple infections can be found. SLE patients also have a higher incidence of cervical dysplasia than the general population. HPV vaccination can be safely administered in SLE patients with stable disease and was shown to be reasonably immunogenic. HPV vaccination should be encouraged in female SLE patients aged 11-14 years. Vaccination can be recommended up to the age of 26 years.

**Reference**

5.2.8 Herpes zoster vaccine (HZ vaccine)

The Advisory Committee on Immunization Practices (ACIP) states that "short-term corticosteroid therapy (<14 days); low-to-moderate dose (<20 mg/day of prednisone or equivalent); topical (e.g., nasal, skin, inhaled); intra-articular, bursal, or tendon injections; or long-term alternate-day treatment with low to moderate doses of short-acting systemic corticosteroids are not considered to be sufficiently immunosuppressive to cause concerns for vaccine safety. Persons receiving this dose or schedule can receive zoster vaccine. Therapy with low-doses of methotrexate (<0.4 mg/Kg/week), azathioprine (<3.0 mg/Kg/day), or 6-mercaptopurine (<1.5 mg/Kg/day) for treatment of rheumatoid arthritis, psoriasis, polymyositis, sarciodosis, inflammatory bowel disease, and other conditions are also not considered sufficiently immunosuppressive to create vaccine safety concerns and are not contraindications for administration of zoster vaccine" (128).

**Conclusion:** At the moment Herpes zoster vaccine is not available in Switzerland. If it is available in the future ACIP recommendations may be followed.

**Reference**

5.2.9 Yellow Fever vaccine

Re-vaccination against yellow fever was safe in 70 patients with rheumatic diseases (11 of these with SLE and 2 with systemic sclerosis) under therapy with MTX, corticosteroids, sulfasalazine, lefunomide, cyclophosphamide and biological agents (129).

**Conclusion:** Due to a lack of data and the theoretical risk of an infection through administration of an actively replicating live vaccine in patients under immunosuppressive therapy, yellow fever vaccination (primary and revaccination) is contraindicated under high-dose corticosteroid therapy, therapy with non-biological or biological DMARDs.

Check travel plans before starting the immunosuppressive therapy. A live vaccine should be administered 3-4 weeks before initiation of therapy. Otherwise it is advisable to wait for at least 4 weeks after discontinuation of high-dose corticosteroid therapy, wait in general for at least 3 months after discontinuation of non-biological DMARD, and at least 3 months after discontinuation of a biological agent (see section 5).

Discourage travelling to a yellow fever endemic country if yellow fever vaccination is not possible.

**Reference**


In patients with connective tissue diseases, there are no published data on vaccccinations against: polio, diphtheria, hepatitis A, measles, mumps, rubella, varicella, tick borne encephalitis, rabies, meningococcal vaccine (polysaccharide or conjugate), japanese encephalitis (inactivated), typhoid fever (parenteral), typhoid fever (oral), cholera.

When no data are available, the respective recommendations for patients with rheumatoid arthritis can be followed.
5.3 Spondylarthritis

5.3.1 Seasonal Influenza vaccine

Seasonal influenza vaccine was demonstrated to be safe in patients with spondylarthritis (SpA) under treatment with corticosteroids, non-biological DMARDs and TNF blocking agents (89).

Immunogenicity of influenza vaccine in SpA patients under corticosteroid treatment and non-biological DMARDs was demonstrated in one study (89). Influenza vaccine was shown to be immunogenic, but less immunogenic under TNF blocking therapy (89).

**Conclusion:** Influenza vaccination can be safely administered in patients with spondylarthritis. It appears to be sufficiently immunogenic under corticosteroids and non-biological therapy. Influenza vaccination induced adequate protection rates in patients treated with TNF-blockers, although post-vaccination antibody titres were reduced.

Insist on checking the vaccination status of household and other close contacts. If they have not received the current seasonal influenza vaccine encourage them to be vaccinated.

References

5.3.2 H1N1 Vaccine

H1N1 vaccination could be safely administered to patients with spondylarthritis (Ankylosing spondylitis and psoriatic arthritis) under treatment with corticosteroids, non-biological DMARDs, TNFα blocking agents and abatacept (100,101,103,105).

Immunogenicity of H1N1 vaccine was demonstrated in a study for SpA patients under corticosteroid treatment (105). But reduced immunogenicity under corticosteroid treatment was demonstrated in another study (103). Reduced immunogenicity was demonstrated under MTX, rituximab and abatacept (100,101). The vaccine was immunogenic in patients under treatment with other non-biologic DMARDs, corticosteroids or TNF blockers in one study (100), but reduced immunogenicity was demonstrated in another study under treatment with non biological DMARDs, such as MTX, leflunomide and immunosuppressive drugs (azathioprin/mycophenolate/CYC) (101). Reduced immunogenicity was demonstrated for adalimumab and infliximab, but not for etanercept (105). In one study, after a second dose, antibody titers and seroprotection rates in patients were similar to those in controls achieved after a first vaccination inspite of the inhibitory effect of several DMARDs and B-cell depletion (101).

**Conclusion:** H1N1 vaccination can be safely administered in patients with spondylarthritis. Immunogenicity may be reduced under corticosteroids, non-biological and biological treatment.

Under B-cell depleting therapy (rituximab), immune responses are probably insufficient when the vaccine is administered within 1-3 months after RTX. Also inactivated vaccinations should be given before initiation of therapy, or 6-8 months afterwards.

If possible, influenza vaccination against new influenza strains vaccination should be given before abatacept treatment.

For new influenza strains and individuals that have not been vaccinated against influenza before two vaccinations should be considered.

**References**


5.3.3 Pneumococcal polysaccharide vaccine and conjugate vaccine

Pneumococcal polysaccharide vaccine and conjugate vaccine could be safely administered in patients with spondylarthritis. (112,114,154–156)

The immunogenicity of pneumococcal polysaccharide vaccination was not reduced by corticosteroids and not by etanercept, but by MTX treatment (154). One study showed that the humoral immune response to the polysaccharide vaccination was not hampered by TNF Alpha blockers (156). The immunogenicity was slightly reduced in patients treated with infliximab or etanercept, but a clear antibody response was elicited in all vaccinated persons (157). One study showed a reduced immune response to the polysaccharide vaccine under TNF Alpha blocker (114). Immune responses to polysaccharide vaccine were reduced in healthy subjects, especially when vaccinated 2 weeks after abatacept treatment (116).

MTX treatment was also associated with lower antibody responses after 7-valent pneumococcal conjugate vaccination in SpA patients. There was not sufficient evidence that TNF blockers reduced the immune response to the conjugate vaccine (112). In one study, the humoral immune response in patients with spondylarthritis treated with TNF blocking agents, was impaired after vaccination with T cell dependent vaccines (Hepatitis B and Pneumococcal conjugate), but not when vaccinated with pneumococcal polysaccharide vaccine (156). Alcohol consumption and smoking were not found to have an effect on the response to pneumococcal conjugate vaccine (155).

Conclusion: Pneumococcal polysaccharide vaccination can be safely administered to patients with spondylarthritis. In general, immunogenicity after vaccination is satisfactory. But methotrexate seems to have a negative effect on both, conjugate and polysaccharide vaccines. Pneumococcal vaccination should be given before abatacept treatment.

The conjugate vaccine should be preferred over polysaccharide vaccinations as conjugate vaccinations produce higher affinity antibody responses, longer lasting immune responses, and the production of memory B cells. Booster vaccinations after conjugate vaccinations are possible while in polysaccharide vaccines secondary vaccines may elicit only poor immune responses due to a lack of memory cells. The administration of a first dose of plain polysaccharide vaccine may blunt the immune response to subsequent doses, such that the antibody levels following a second vaccination, and possibly the magnitude of clinical protection, may be lower than following a first vaccination.

References


5.3.4 Hepatitis B

TNF blocking therapy severely impaired the antibody response to T cell dependent hepatitis B vaccination in SpA patients. TNF blockers were shown to interfere with the affinity maturation and differentiation of activated B cells towards antibody producing cells (156,157).

Conclusion: Hepatitis B vaccination can be safely administered to SpA patients. As there are insufficient data on the immunogenicity of hepatitis B vaccination in SpA patients under immunosuppressive treatments, a serology should be performed 4-6 weeks after vaccination in immunosuppressed SpA patients and, if necessary, further doses should be administered.

Reference


5.3.5 Hepatitis A vaccine

The immunogenicity of hepatitis A vaccination was studied in 56 immunocompromised travellers, out of which 9% had psoriasis. 43% of all patients under methotrexate, 28% of those under corticosteroid therapy and 20% of the patients under TNF blocking therapy, as well as both patients treated with Tacrolism did not develop sufficient hepatitis A antibodies (122).

**Conclusion:** Hepatitis A vaccination can be safely administered to SpA patients. As there are insufficient data on the immunogenicity of hepatitis A vaccination in SpA patients, a serology should be performed 4-6 weeks after vaccination in immunosuppressed SpA patients.

If short term protection is necessary, a serology can be performed 4-6 weeks after the first dose and if necessary a second dose can be administered at a short interval.

For long-term protection, a serology should be performed 4-6 weeks after the regular second dose (dose 6 months after the first dose) and if necessary further vaccine doses should be administered.

**References**

5.3.6 Herpes zoster vaccine

Out of 463'541 medicare beneficiaries (292'169 with RA, 89'565 psoriasis, 4'026 ankylosing spondylitis, 66'751 inflammatory bowel disease) 18'683 (4%) received the HZ vaccine. Patients were treated with TNF-α inhibitors, non-TNF-α biologic drugs, DMARDs and/or corticosteroids. A retrospective analysis showed that the receipt of HZ vaccine was not associated with an increase of HZ infections up to 42 days after vaccination. In the long-term (2 years of follow-up) the vaccination was associated with a protective effect (127).

The Advisory Committee on Immunization Practices (ACIP) states that “short-term corticosteroid therapy (<14 days); low-to-moderate dose (<20 mg/day of prednisone or equivalent); topical (e.g., nasal, skin, inhaled); intra-articular, bursal, or tendon injections; or long-term alternate-day treatment with low to moderate doses of short-acting systemic corticosteroids are not considered to be sufficiently immunosuppressive to cause concerns for vaccine safety. Persons receiving this dose or schedule can receive zoster vaccine. Therapy with low-doses of methotrexate (<0.4 mg/Kg/week), azathioprine (<3.0 mg/Kg/day), or 6-mercaptopurine (<1.5 mg/Kg/day) for treatment of rheumatoid arthritis, psoriasis, polymyositis, sarcoidosis, inflammatory bowel disease, and other conditions are also not considered sufficiently immunosuppressive to create vaccine safety concerns and are not contraindications for administration of zoster vaccine” (128).

Conclusion: At the moment Herpes zoster vaccine is not available in Switzerland. If it is available in the future ACIP recommendations may be followed.

Reference


5.3.7 Yellow Fever vaccine

Re-vaccination against yellow fever was safe in 70 patients with rheumatic diseases (5 of these with SpA) under therapy with MTX, corticosteroids, sulfasalazine, leflunomide, cyclophosphamide and biological agents (129).

Conclusion: Due to a lack of data and the theoretical risk of an infection through administration of an actively replicating live vaccine in patients under immunosuppressive therapy yellow fever vaccination (primary and revaccination) is contraindicated under high-dose corticosteroid therapy, therapy with non-biological or biological DMARDs.

Check travel plans before starting the immunosuppressive therapy. A live vaccine should be administered 3-4 weeks before initiation of therapy. Otherwise it is advisable to wait for at least 4 weeks after discontinuation of high-dose corticosteroid therapy, wait in general for at least 3 months after discontinuation of non-biological DMARD, and at least 3 months after discontinuation of a biological agent before the administration of YF vaccination (see section 5).

Discourage travelling to a yellow fever endemic country if yellow fever vaccination is not possible.

Reference


In patients with spondylarthritis, there are no published data on vaccinations against: tetanus, diphtheria, polio, measles, mumps, rubella, varicella, Haemophilus influenzae b, human papillomavirus, tick borne encephalitis, rabies, meningococcal vaccine (polysaccharide or conjugate), japanese encephalitis (inactivated), typhoid fever (parenteral), typhoid fever (oral), cholera.

When no data are available, the respective recommendations for patients with rheumatoid arthritis can be followed.
5.4 Vasculitis

5.4.1 Seasonal Influenza vaccine

Seasonal influenza vaccination was shown to be safe in patients with Wegener’s granulomatosis without medication and under treatment with corticosteroids and non-biological DMARDs (158,159).

Seasonal influenza vaccination was shown to be immunogenic in patients with Wegener’s granulomatosis treated with corticosteroids and non-biological DMARDs (158,159).

**Conclusion:** Influenza vaccination can be safely administered in patients with vasculitis. It is sufficiently immunogenic under corticosteroids and non-biological DMARDs.

Insist on checking the vaccination status of household and other close contacts. If they have not received the current seasonal influenza vaccine encourage them to be vaccinated.

**References**


5.4.2 H1N1 vaccine

H1N1 vaccination could be safely administered to patients with vasculitis (100,101,138).

One study demonstrated immunogenicity of H1N1 vaccine in patients with systemic necrotising vasculitis patients (138). One study showed that H1N1 vaccination was immunogenic in patients with Takayasu arteritis patients, but less immunogenic in patients with Wegener’s granulomatosis or Behçet’s disease (103). In two studies, MTX, rituximab and abatacept had a negative effect on the immune response (100,101). Reduced immunogenicity was also demonstrated under treatment with other non-biological DMARDS, such as leflunomide, azathioprine, mycophenolate and CYC. After a second dose, antibody titers and seroprotection rates in patients were similar to those in controls achieved after a first vaccination in spite of the inhibitory effect of several DMARDS and B-cell depletion (101).

**Conclusion:** H1N1 vaccination can be safely administered in patients with vasculitis. Immunogenicity may be reduced.

Under B-cell depleting therapy (rituximab), immune responses are probably insufficient when the vaccine is administered within 1-3 months after RTX. Also inactivated vaccinations should be given before initiation of therapy, or 6-8 months afterwards.

If possible, influenza vaccination against new influenza strains vaccination should be given before abatacept treatment.

For new influenza strains and individuals that have not been vaccinated against influenza before two vaccinations should be considered.

**References**


5.4.3 Pneumococcal polysaccharide vaccine

In one publication, severe safety issues were raised after pneumococcal vaccination in patients with Behçet’s disease. It was reported that pneumococcal polysaccharide vaccination caused severe local reaction in 4/4 patients with Behçet’s disease and severe systemic reactions in 3/4 patients with Behçet’s disease. One patient was treated with abatacept and Prednisolone, one patient with etanercept, one patient with Ibuprofen and one patient with azathioprine (160). It was hypothesized, that the pneumococcal vaccine can activate toll-like receptors (TLRs) 2 and 4 as known activators of the inflammasome activation.

Immune responses to pneumococcal polysaccharide vaccine were reduced in healthy subjects under abatacept, esp. when vaccinated 2 weeks after abatacept treatment (116).

**Conclusion:** Data from case reports indicate that pneumococcal polysaccharide vaccination in patients with Behçet’s disease may be associated with severe adverse reactions, but data from well-designed controlled studies are missing. The vaccination of patients with against pneumococcal disease requires special attention.

In patients with vasculitis other than Behçet’s disease there are no safety concerns, although data are missing. Under B-cell depleting therapy (rituximab), immune responses are probably insufficient when vaccine is administered within 1-3 months after RTX. Pneumococcal vaccination should be given before initiation of therapy, or 6-8 months afterwards. If possible, pneumococcal vaccination should be given before abatacept treatment.

**Reference**


5.4.4 Hepatitis B vaccine

One study demonstrated that hepatitis B vaccine could be safely administered to 13 patients with Behçet’s disease treated with Colchicine (161).

In this study, the majority of Behçet’s disease developed seroprotective antibodies after the regular hepatitis B vaccination course. One patient who had not responded after the regular course responded after 3 additional vaccinations.

**Conclusion:** Hepatitis B vaccination can be safely administered to patients with vasculitis. As there are insufficient data on the immunogenicity of hepatitis B vaccination in patients with vasculitis, a serology should be performed 4-6 weeks after vaccination in immunosuppressed patients and, if necessary, further doses should be administered.

**Reference**


In patients with vasculitis, there are no published data on vaccinations against: tetanus, polio, diphtheria, hepatitis A, measles, mumps, rubella, varicella, *Haemophilus influenzae* b, human papillomavirus, tick borne encephalitis, rabies, meningococcal vaccine (polysaccharide or conjugate), japanese encephalitis (inactivated), typhoid fever (parenteral), typhoid fever (oral), cholera, yellow fever.

When no data are available, the respective recommendations for patients with rheumatoid arthritis can be followed.
6 Timing of Vaccination in relation to disease activity

No studies have been performed comparing immunogenicity and safety of vaccinations between patients with AIIRD with stable and unstable disease. Moreover, almost all vaccination studies in AIIRD patients were performed in patients with stable disease.

In several studies on influenza and pandemic influenza vaccine, no increase in side effects or disease flares, or decreased vaccine immunogenicity was seen when also patients with moderate or severe disease activity were included (95,100,103).

In two studies, one on pneumococcal, tetanus toxoid and Haemophilus influenzae type b in patients with SLE, and one study on hepatitis B vaccination in patients with RA, the immunogenicity seemed to be reduced in patients with increased disease activity. This effect might also be attributed to the fact that patients with higher disease activity also received more immunosuppressive therapy (120,145).

However, the numbers of patients in these studies were too small to draw a definite conclusion.

Conclusion: Therefore, based on theoretical risks of disease flares following vaccination in unstable patients with AIIRD and a reduced immunogenicity due to a higher level of immunosuppressive therapy during unstable disease, vaccination should preferentially be administered during stable disease.

References


7 Timing of vaccination in relation to medication

7.1 Inactivated vaccines

Timing of vaccination in relation to medication has been shown to influence the immunogenicity of inactivated vaccines. This effect has been demonstrated for infliximab, and rituximab in AIIRD patients and for abatacept in healthy subjects.

**Infliximab:** In one study in patients with rheumatoid arthritis, the timing of influenza vaccination in relation to infliximab influenced the immunogenicity of the vaccine (88). The antibody response was reduced when the vaccination was administered 3 weeks after the infliximab infusion, but it was not reduced when the vaccine was given on the same day as the infusion.

**Rituximab:** Also under rituximab treatment, the timing of vaccination in relation to RTX treatment was shown to be important. When influenza vaccination was administered to RA patients 84 days after RTX treatment, the immune response was blunted (98). It was shown that B cells were completely depleted from day 28 to day 84 after RTX infusion (98). The humoral immune response was partly restored when the influenza vaccine was administered 6-10 months after RTX treatment (99). In another study, influenza vaccination was less, but still sufficiently, immunogenic in patients under RTX treatment (90). But the time point of RTX treatment in relation to vaccination is not exactly reported.

The immunogenicity of H1N1 vaccine was especially reduced in RA and CTD patients when the vaccination was administered after recent anti-CD20 antibody rituximab treatment (<12 weeks) (101). The combination of RTX + MTX hampered the immune response to pneumococcal polysaccharide vaccine in RA patients (107), when the vaccine was administered 24 weeks after RTX treatment.

Antibody responses to tetanus toxoid vaccination (i.e. a ≥ 4-fold rise in antibodies) were similar in those RA patients treated with RTX plus MTX or with MTX alone (39.1% vs. 42.3%) (107). That means, RTX treatment in addition to MTX did not have a negative effect on the immune response to the T cell dependent tetanus toxoid vaccine, when the vaccine was administered 24 weeks after RTX treatment.

**Abatacept:** Immune responses to pneumococcal polysaccharide vaccine were reduced in healthy subjects under abatacept therapy. The effect was strongest in those subjects who were vaccinated 2 weeks after abatacept treatment. In those who were vaccinated before the administration of abatacept the effect was minor (116).

Immune responses to tetanus toxoid vaccine were reduced in healthy subjects under abatacept therapy. The effect was strongest in those subjects who were vaccinated 2 weeks after abatacept treatment. In those who were vaccinated before the administration of abatacept the effect was minor (116).

**Conclusion:** Immunogenicity of inactivated vaccines may be preserved when administered on the same day as infliximab infusion, but may be hampered when administered several weeks afterwards, when the full immunosuppressive effect has taken place. More data will necessary for a reliable recommendation regarding the timing if vaccination and infliximab infusions.

Under B-cell depleting therapy (rituximab), immune responses to inactivated are probably insufficient when a vaccine is administered within 1-3 months after RTX. For inducing a better immunogenicity, inactivated vaccinations should be given before initiation of therapy, or 6-8 months afterwards.

If possible, inactivated vaccinations should be given at least 2 weeks before abatacept treatment to induce a sufficient immunogenicity.

**References**


7.2 Live vaccines

For safety reasons, it is advisable to wait for a certain time period after the administration of an immunosuppressive agent before the administration of a live vaccine. In the literature no infection of a patient with a rheumatic disease by the administration of a live vaccine has been reported. But due to a theoretical risk of replication and infection of an AIIRD patient by administering a live vaccine, live vaccines should in general be avoided during immunosuppressive treatment and for the duration of the ongoing immunosuppressive effect after cessation or pausing of the immunosuppressive medication.

The duration of the immunosuppressive effect depends on (i) the half-life of the active drug component and (ii) recovery from the immunological effect (e.g. depleting cytotoxic effect caused by apoptosis or clonal deletion of B- or T- cells). For most immunosuppressive medications this time point has not been clearly defined(162).

There are some general conclusions:
Table 1: Time period between cessation or pausing of an immunosuppressive agent and administration of live vaccines

<table>
<thead>
<tr>
<th>Medication</th>
<th>Herpes Zoster vaccine</th>
<th>MMR vaccine, Varicella vaccine, Yellow Fever vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>can always be given</td>
<td>can always be given</td>
</tr>
<tr>
<td>• Short- or long-term daily or alternate-day therapy with &lt;20 mg of prednisone or equivalent or 0.5mg/kg/day of prednisone or equivalent in children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Maintenance physiologic doses (replacement therapy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Topical steroids (airways, skin, ears, or eyes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Intraarticular, bursal, or tendon injection of steroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• high-dose steroids (≥20 mg per day of prednisone or equivalent or 0.5mg/kg/day of prednisone or equivalent in children for &gt;2 weeks)</td>
<td>wait at least 1 month after cessation</td>
<td>wait at least 1 month</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>wait at least 3 months</td>
<td>wait at least 3 months*</td>
</tr>
<tr>
<td>Ciclosporine A</td>
<td>wait at least 3 months</td>
<td>wait at least 3 months*</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>wait at least 3 months</td>
<td>wait at least 3 months*</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>wait at least 3 months</td>
<td>wait at least 3 months*</td>
</tr>
<tr>
<td>Infliximab</td>
<td>wait at least 3 months</td>
<td>wait at least 3 months*</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>wait at least 3 months</td>
<td>wait at least 3 months*</td>
</tr>
<tr>
<td>Golimumab</td>
<td>wait at least 3 months</td>
<td>wait at least 3 months*</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>wait at least 3 months</td>
<td>wait at least 3 months*</td>
</tr>
<tr>
<td>Abatacept</td>
<td>wait at least 3 months</td>
<td>wait at least 3 months*</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>wait at least 3 months</td>
<td>wait at least 3 months*</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>wait at least 3 months</td>
<td>wait at least 3 months*</td>
</tr>
<tr>
<td>Anakinra</td>
<td>wait at least 3 months*</td>
<td>wait at least 3 months*</td>
</tr>
<tr>
<td>Etanercept</td>
<td>wait at least 3 months, in clinically stable cases live vaccines can be given at an earlier stage, &gt; 1 month after stopping etanercept</td>
<td>wait at least 3 months, in clinically stable cases live vaccines can be given at an earlier stage, &gt; 1 month after stopping etanercept</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>&lt;0.4 mg/kg/week (&lt; 20mg/m²/week): can be given</td>
<td>wait at least 3 months, in clinically stable cases live vaccines can be given during low dosage therapy: methotrexate &lt; 20mg/m²/week</td>
</tr>
<tr>
<td></td>
<td>≥0.4 mg/kg/week (≥ 20mg/m²/week): &gt; 3 months</td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>&lt;3.0 mg/kg/day: can be given</td>
<td>wait at least 3 months</td>
</tr>
<tr>
<td></td>
<td>≥3.0 mg/kg/day: &gt; 3 months</td>
<td></td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>&lt;1.5 mg/kg/day: can be given</td>
<td>wait at least 3 months</td>
</tr>
<tr>
<td></td>
<td>≥1.5 mg/kg/day: &gt; 3 months</td>
<td></td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>No restrictions (163)</td>
<td>No restrictions (163)</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>wait at least 2 years**</td>
<td>&gt; 2 years**</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>wait at least &gt;12 months</td>
<td>&gt;12 months</td>
</tr>
<tr>
<td>Rituximab</td>
<td>wait at least &gt;12 months</td>
<td>&gt;12 months</td>
</tr>
</tbody>
</table>

* due to the short half-life (4-6 hours) of Anakinra, live vaccines might be given earlier than 3 months after cessation of the therapy. But so far, only data on the safe and immunogenic administration of a second MMR vaccination in three cases after cessation of Anakinra for 5 half-lives have been reported (125). ** after consultation with a specialist washout with Colesytyramin or activated carbon can be considered to shorten the time interval.
References


8 Effect of an additional vaccine dose

**H1N1 vaccination:** It could be shown that with a second vaccine dose, administered 3-4 weeks after the first dose, similar antibody titers and seroprotection rates (>70%) could be achieved in RA, CTD, SpA and vasculitis patients compared to those in controls inspite of the inhibitory effect of several non-biological and biological DMARDs (incl. B-cell depletion) (101).

In another study, if antibody response was not observed to the first subcutaneously administered H1N1 vaccination, a booster vaccination could produce seroprotection in 33% of RA patients (102).

In a study by Mathian et al., in SLE patients without immunosuppressive treatment and with a lymphocyte count > 1.0x10^9/liter all immunogenicity criteria were met after one H1N1 vaccination (seroconversion rate, seroprotection rate, GMT fold increase). A booster vaccine increased the three criteria, but not "significantly". In SLE patients on immunosuppressive treatment, only one immunogenicity criterium was met after the first H1N1 dose and in SLE patients with a lymphocyte count ≤1.0x10^9/liter two criteria were met. In these two subgroups the booster vaccination was beneficial in terms of immunogenicity as an additional immunogenicity criterion was met after the 2nd dose (143).

**Hepatitis B vaccination:** In a study by Kuruma et al., hepatitis B vaccination induced adequate humoral immune responses in SLE patients with inactive disease. 2/28 (7%) patients did not seroconvert after the 3rd dose and received another dose. After the fourth dose positive anti-HBs were detected. None of the patients received immunosuppressive treatments or glucocorticoids > 20mg/day (152). In one study hepatitis B vaccine was administered to 13 patients with Behçet’s disease treated with Colchicine. In this study, the majority of Behçet’s disease developed seroprotective antibodies after the regular hepatitis B vaccination course. One patient who had not responded after the regular course responded after 3 additional vaccinations (161).

**Conclusion:** As there are insufficient data on the immunogenicity of hepatitis B vaccination in patients with vasculitis, a serology should be performed 4-6 weeks after vaccination in immunosuppressed patients and, if necessary, further doses should be administered. Some patients may respond after additional doses.

A booster dose 3-4 weeks after the first dose may be considered for new influenza strains or patients that have not been vaccinated against influenza before.

**References**


9 All references


71. CDC - Veterans Health - Gulf War Studies - Defining Gulf War Illness. [cited 2013 May 21]; Available from: http://www.cdc.gov/nceh/veterans/default2g.htm


