Background document on

Immune-mediated inflammatory diseases (IMID)

Module 1

Vaccination in patients with autoimmune inflammatory rheumatic diseases (AIIRD)

Document

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Abbreviations

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

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 Unpublished (grey) literature (unpublished reports, conference abstracts) was retrieved through a targeted website search of relevant organizations and international conferences dealing with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:

Autoimmune inflammatory rheumatic diseases: “rheumatology”, “rheumatic”, “AIIRD”, “autoimmune”, “immunocompromised”, “autoimmune inflammatory rheumatic disease”, “rheumatoid arthritis”, “lupus erythematosus”, “spondylarthritis”, “vasculitis”, “connective tissue disease”, “ scleroderma”, “systemic sclerosis”, “Behçet’s disease”, “Wegener granulomatosis”, “Churg-Strauss syndrome” , “Dermatomyositis”, “Polymyositis”, “Polyarteriitis nodosa” “Takayasu arteritis”, “Giant cell arteritis”, “Psoriatic arthritis”

Infections: “infection”, “risk of infection”, “tetanus”, “diphtheria”, “poliomyelitis”, “polio”, “pertussis”, “hepatitis A”, “hepatitis B”, “haemophilus influenza b”, “yellow fever”, “mumps”, “measles”, “rubella”, “varicella”, “herpes zoster” “rabies”, “tick borne encephalitis”, “TBE”, “Japanese encephalitis”, “cholera”, “human papillomavirus”, “HPV”, “typhoid fever”, “meningococcal” “pneumococcal”, “influenza”, “H1N1”, “tuberculosis”

Vaccines: “vaccination”, “vaccine”, “vaccination guideline”, “inactivated vaccine”, “live vaccine”, “conjugate vaccine”, “polysaccharide vaccine”, “tetanus vaccine*”, “diphtheria vaccine*”, “poliomyelitis vaccine*”, “polio vaccine*”, “pertussis vaccine*”, “hepatitis A vaccine*”, “hepatitis B vaccine*”, “haemophilus influenza b vaccine*”, “yellow fever vaccine*”, “mumps vaccin*”, “measles vaccin* ”, “rubella vaccin*”, “varicella vaccin*”, “herpes zoster vaccin*” “rabies vaccin*”, “tick borne encephalitis vaccin*”, “TBE vaccine*”, “Japanese encephalitis vaccin*”, “cholera vaccin*”, “human papillomavirus vaccin*”, “HPV vaccin*”, “typhoid fever vaccin*”, “meningococcal vaccin*” “pneumococc* vaccin*”, “influenza vaccin*”, “H1N1 vaccin*”, “tuberculosis vaccin*”, “BCG”

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 AIIIRD 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 (AIIRD) (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

1. Bijl M, Kallenberg CG, van Assen S. Vaccination of the immune-compromised patients with focus on patients with autoimmune-inflammatory diseases. Neth J Med [Internet]. 2011/02/18 ed. 2011;69(1):5–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21325695

2. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum [Internet]. 2002/10/02 ed. 2002;46(9):2287–93. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12355475

3. Wagner UG, Koetz K, Weyand CM, Goronzy JJ. Perturbation of the T cell repertoire in rheumatoid arthritis. Proceedings of the National Academy of Sciences of the United States of America [Internet]. 1998 Nov 24 [cited 2012 Nov 7];95(24):14447–52. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=24393&tool=pmcentrez&rendertype=abstract

4. Koetz K, Bryl E, Spickschen K, O'Fallon WM, Goronzy JJ, Weyand CM. T cell homeostasis in patients with rheumatoid arthritis. Proceedings of the National Academy of Sciences of the United States of America [Internet]. 2000 Aug 1 [cited 2012 Nov 7];97(16):9203–8. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=16846&tool=pmcentrez&rendertype=abstract

5. Peter H-H, Pichler WJ, Müller-Ladner U. Klinische Immunologie. Urban & Fischer Bei Elsev; 2012.

6. Bernatsky S, Hudson M, Suissa S. Anti-rheumatic drug use and risk of serious infections in rheumatoid arthritis. Rheumatology (Oxford) [Internet]. 2007/05/05 ed. 2007;46(7):1157–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17478469

7. Gluck T, Kiefmann B, Grohmann M, Falk W, Straub RH, Scholmerich J. Immune status and risk for infection in patients receiving chronic immunosuppressive therapy. J Rheumatol [Internet]. 2005/08/04 ed. 2005;32(8):1473–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16078322

8. Salliot C, Gossec L, Ruyssen-Witrand A, Luc M, Duclos M, Guignard S, et al. Infections during tumour necrosis factor-alpha blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients. Rheumatology (Oxford) [Internet]. 2006/08/02 ed. 2007;46(2):327–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16880188

9. Curtis JR, Patkar N, Xie A, Martin C, Allison JJ, Saag M, et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum [Internet]. 2007/03/30 ed. 2007;56(4):1125–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17393394

10. Listing J, Strangfeld A, Kary S, Rau R, von Hinueber U, Stoyanova-Scholz M, et al. Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum [Internet]. 2005/10/29 ed. 2005;52(11):3403–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16255017

11. Bernatsky S, Habel Y, Rahme E. Observational studies of infections in rheumatoid arthritis: a metaanalysis of tumor necrosis factor antagonists. J Rheumatol [Internet]. 2010/04/03 ed. 2010;37(5):928–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20360181

12. Salmon-Ceron D, Tubach F, Lortholary O, Chosidow O, Bretagne S, Nicolas N, et al. Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. Ann Rheum Dis [Internet]. 2010/12/24 ed. 2011;70(4):616–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21177290

13. Curtis JR, Xie F, Chen L, Baddley JW, Beukelman T, Saag KG, et al. The comparative risk of serious infections among rheumatoid arthritis patients starting or switching biological agents. Ann Rheum Dis [Internet]. 2011/05/19 ed. 2011;70(8):1401–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21586439

14. Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. Ann Rheum Dis [Internet]. 2008/01/22 ed. 2009;68(1):25–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18203761

15. Singh J, Wells G, Christensen R, Tanjong Ghogomu E, Maxwell L, Jk M, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview (Review). Cochrane Database Syst Rev. 2011 Feb 16;(2):CD008794

16. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine [Internet]. 2003 Sep [cited 2012 Nov 7];82(5):299–308. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14530779

17. Ruangjutipopan S, Kasitanon N, Louthrenoo W, Sukitawut W, Wichainun R. Causes of death and poor survival prognostic factors in thai patients with systemic sclerosis. Journal of the Medical Association of Thailand = Chotmaihet thangphaet [Internet]. 2002 Nov [cited 2012 Nov 7];85(11):1204–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12546318

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

18. Blumentals WA, Arreglado A, Napalkov P, Toovey S. Rheumatoid arthritis and the incidence of influenza and influenza-related complications: a retrospective cohort study. BMC Musculoskelet Disord [Internet]. 2012/08/29 ed. 2012;13(1):158. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22925480

19. Nichol KL, Wuorenma J, von Sternberg T. Benefits of influenza vaccination for low-, intermediate-, and high-risk senior citizens. Arch Intern Med [Internet]. 1998/09/17 ed. 1998;158(16):1769–76. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9738606

20. Hak E, Nordin J, Wei F, Mullooly J, Poblete S, Strikas R, et al. Influence of high-risk medical conditions on the effectiveness of influenza vaccination among elderly members of 3 large managed-care organizations. Clin Infect Dis [Internet]. 2002/07/30 ed. 2002;35(4):370–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12145718

21. Dirven L, Huizinga T, Allaart C. Risk factors for reported influenza and influenza-like symptoms in patients with rheumatoid arthritis. Scand J Rheumatol [Internet]. 2012/07/21 ed. 2012; Available from: http://www.ncbi.nlm.nih.gov/pubmed/22813350

22. Wotton CJ, Goldacre MJ. Risk of invasive pneumococcal disease in people admitted to hospital with selected immune-mediated diseases: record linkage cohort analyses. Journal of epidemiology and community health [Internet]. 2012 Dec 6 [cited 2012 Nov 8];66(12):1177–81. Available from: http://jech.bmj.com/content/early/2012/04/05/jech-2011-200168.full

23. Choi HJ, Kim MY, Kim HO, Park YM. An atypical varicella exanthem associated with the use of infliximab. Int J Dermatol [Internet]. 2006/08/17 ed. 2006;45(8):999–1000. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16911403

24. Vonkeman H, ten Napel C, Rasker H, van de Laar M. Disseminated primary varicella infection during infliximab treatment. J Rheumatol [Internet]. 2004/12/01 ed. 2004;31(12):2517–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15570661

25. Lee DH, Kim HS, Song YW, Cho KH. Development of varicella during adalimumab therapy. J Eur Acad Dermatol Venereol [Internet]. 2007/04/24 ed. 2007;21(5):687–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17447988

26. Wolfe F, Michaud K, Chakravarty EF. Rates and predictors of herpes zoster in patients with rheumatoid arthritis and non-inflammatory musculoskeletal disorders. Rheumatology (Oxford) [Internet]. 2006/09/28 ed. 2006;45(11):1370–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17003175

27. Strangfeld A, Listing J, Herzer P, Liebhaber A, Rockwitz K, Richter C, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. JAMA [Internet]. 2009/02/20 ed. 2009;301(7):737–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19224750

28. Smitten AL, Choi HK, Hochberg MC, Suissa S, Simon TA, Testa MA, et al. The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. Arthritis Rheum [Internet]. 2007/12/01 ed. 2007;57(8):1431–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18050184

29. Manzi S, Kuller LH, Kutzer J, Pazin GJ, Sinacore J, Medsger TA, et al. Herpes zoster in systemic lupus erythematosus. The Journal of rheumatology [Internet]. 1995 Jul [cited 2012 Nov 7];22(7):1254–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7562754

30. Galloway JB, Mercer LK, Moseley A, Dixon WG, Ustianowski AP, Helbert M, et al. Risk of skin and soft tissue infections (including shingles) in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Annals of the rheumatic diseases [Internet]. 2012 Apr 24 [cited 2012 Nov 8];annrheumdis–2011–201108–. Available from: http://ard.bmj.com/content/early/2012/04/23/annrheumdis-2011-201108.long

31. García-Doval I, Pérez-Zafrilla B, Descalzo MA, Roselló R, Hernández MV, Gómez-Reino JJ, et al. Incidence and risk of hospitalisation due to shingles and chickenpox in patients with rheumatic diseases treated with TNF antagonists. Annals of the rheumatic diseases [Internet]. 2010 Oct 1 [cited 2012 Nov 8];69(10):1751–5. Available from: http://ard.bmj.com/content/69/10/1751.long

32. Santana IU, Gomes Ado N, Lyrio LD, Rios Grassi MF, Santiago MB. Systemic lupus erythematosus, human papillomavirus infection, cervical pre-malignant and malignant lesions: a systematic review. Clin Rheumatol [Internet]. 2010/11/13 ed. 2011;30(5):665–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21072553

33. Nath R, Mant C, Luxton J, Hughes G, Raju KS, Shepherd P, et al. High risk of human papillomavirus type 16 infections and of development of cervical squamous intraepithelial lesions in systemic lupus erythematosus patients. Arthritis and rheumatism [Internet]. 2007 May 15 [cited 2012 Nov 8];57(4):619–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17471531

34. Tam L-S, Chan PKS, Ho SC, Yu MMY, Yim S-F, Cheung T-H, et al. Natural history of cervical papilloma virus infection in systemic lupus erythematosus - a prospective cohort study. The Journal of rheumatology [Internet]. 2010 Feb [cited 2012 Nov 7];37(2):330–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20032093

35. Tanaka E, Urata Y. Risk of hepatitis B reactivation in patients treated with tumor necrosis factor-alpha inhibitors. 2011/12/14 ed. 2012;42(4):333–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22150950

36. World Tourism Organization, (UNWTO). International tourism on track to hit one billion by end of 2012 [Internet]. [cited 2012 Nov 8]. Available from: http://media.unwto.org/en/press-release/2012-09-12/international-tourism-track-hit-one-billion-end-2012

37. Bundesamt für Statistik. Reisen der Schweizer Wohnbevölkerung. Neuchâtel, Switzerland; 2010.

38. Wieten RW, Leenstra T, Goorhuis A, van Vugt M, Grobusch MP. Health risks of travelers with medical conditions--a retrospective analysis. Journal of travel medicine [Internet]. [cited 2012 Nov 8];19(2):104–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22414035

39. Baaten GG, Geskus RB, Kint JA, Roukens AH, Sonder GJ, van den Hoek A. Symptoms of infectious diseases in immunocompromised travelers: a prospective study with matched controls. J Travel Med [Internet]. 2011/09/08 ed. 2011;18(5):318–26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21896095

40. Seong SS, Choi CB, Woo JH, Bae KW, Joung CL, Uhm WS, et al. Incidence of tuberculosis in Korean patients with rheumatoid arthritis (RA): effects of RA itself and of tumor necrosis factor blockers. J Rheumatol [Internet]. 2007/02/20 ed. 2007;34(4):706–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17309133

41. Brassard P, Lowe AM, Bernatsky S, Kezouh A, Suissa S. Rheumatoid arthritis, its treatments, and the risk of tuberculosis in Quebec, Canada. Arthritis Rheum [Internet]. 2009/02/28 ed. 2009;61(3):300–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19248128

42. Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Coster L, et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. Arthritis Rheum [Internet]. 2005/06/30 ed. 2005;52(7):1986–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15986370

43. Tam LS, Li EK, Wong SM, Szeto CC. Risk factors and clinical features for tuberculosis among patients with systemic lupus erythematosus in Hong Kong. Scand J Rheumatol [Internet]. 2002/11/29 ed. 2002;31(5):296–300. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12455821

44. Yun JE, Lee SW, Kim TH, Jun JB, Jung S, Bae SC, et al. The incidence and clinical characteristics of Mycobacterium tuberculosis infection among systemic lupus erythematosus and rheumatoid arthritis patients in Korea. Clin Exp Rheumatol [Internet]. 2002/06/08 ed. 2002;20(2):127–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12051389

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

45. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, Keenlyside RA, Ziegler DW, Retailliau HF, et al. Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976--1977. American journal of epidemiology [Internet]. 1979 Aug [cited 2013 May 21];110(2):105–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/463869

46. Schonberger LB, Hurwitz ES, Katona P, Holman RC, Bregman DJ. Guillain-Barré syndrome: its epidemiology and associations with influenza vaccination. Annals of neurology [Internet]. 1981 Jan [cited 2013 May 21];9 Suppl:31–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7224614

47. Salmon DA, Proschan M, Forshee R, Gargiullo P, Bleser W, Burwen DR, et al. Association between Guillain-Barré syndrome and influenza A (H1N1) 2009 monovalent inactivated vaccines in the USA: a meta-analysis. The Lancet [Internet]. 2013 Mar 12 [cited 2013 Mar 16];381(9876):1461–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23498095

48. Dieleman J, Romio S, Johansen K, Weibel D, Bonhoeffer J, Sturkenboom M. Guillain-Barre syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe. BMJ (Clinical research ed.) [Internet]. 2011 Jan [cited 2013 Mar 19];343:d3908. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3134565&tool=pmcentrez&rendertype=abstract

49. DeStefano F, Vellozzi C, Schonberger LB, Chen RT. Safety of adjuvanted pandemic influenza A (H1N1) 2009 vaccines. BMJ (Clinical research ed.) [Internet]. 2011 Jan [cited 2013 May 21];343:d4159. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21750073

50. Greene SK, Rett M, Weintraub 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

Project, 2009-2010. American journal of epidemiology [Internet]. 2012 Jun 1 [cited 2013 May 21];175(11):1100–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22582210

51. Yih WK, Lee GM, Lieu TA, Ball R, Kulldorff M, Rett M, et al. Surveillance for adverse events following receipt of pandemic 2009 H1N1 vaccine in the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) System, 2009-2010. American journal of epidemiology [Internet]. 2012 Jun 1 [cited 2013 May 21];175(11):1120–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22582207

52. Vellozzi C, Broder KR, Haber P, Guh A, Nguyen M, Cano M, et al. Adverse events following influenza A (H1N1) 2009 monovalent vaccines reported to the Vaccine Adverse Event Reporting System, United States, October 1, 2009-January 31, 2010. Vaccine [Internet]. 2010 Oct 21 [cited 2013 May 18];28(45):7248–55. Available from: http://dx.doi.org/10.1016/j.vaccine.2010.09.021

53. Wise ME, Viray M, Sejvar JJ, Lewis P, Baughman AL, Connor W, et al. Guillain-Barre syndrome during the 2009-2010 H1N1 influenza vaccination campaign: population-based surveillance among 45 million Americans. American journal of epidemiology [Internet]. 2012 Jun 1 [cited 2013 Apr 16];175(11):1110–9. Available from: http://aje.oxfordjournals.org/content/175/11/1110.long

54. Williams SE, Pahud BA, Vellozzi C, Donofrio PD, Dekker CL, Halsey N, et al. Causality assessment of serious neurologic adverse events following 2009 H1N1 vaccination. Vaccine [Internet]. 2011 Oct 26 [cited 2013 May 21];29(46):8302–8. Available from: http://dx.doi.org/10.1016/j.vaccine.2011.08.093

55. Tokars JI, Lewis P, DeStefano F, Wise M, Viray M, Morgan O, et al. The risk of Guillain-Barré syndrome associated with influenza A (H1N1) 2009 monovalent vaccine and 2009-2010 seasonal influenza vaccines: results from self-controlled analyses. Pharmacoepidemiology and drug safety [Internet]. 2012 May [cited 2013 May 21];21(5):546–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22407672

56. Verity C, Stellitano L, Winstone AM, Andrews N, Stowe J, Miller E. Guillain-Barré syndrome and H1N1 influenza vaccine in UK children. Lancet [Internet]. 2011 Oct 29 [cited 2013 May 21];378(9802):1545–6. Available from: http://dx.doi.org/10.1016/S0140-6736(11)61665-6

57. Stowe J, Andrews N, Wise L, Miller E. Investigation of the temporal association of Guillain-Barre syndrome with influenza vaccine and influenzalike illness using the United Kingdom General Practice Research Database. American journal of epidemiology [Internet]. 2009 Feb 1 [cited 2013 May 21];169(3):382–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19033158

58. Andrews N, Stowe J, Al-Shahi Salman R, Miller E. Guillain-Barré syndrome and H1N1 (2009) pandemic influenza vaccination using an AS03 adjuvanted vaccine in the United Kingdom: self-controlled case series. Vaccine [Internet]. 2011 Oct 19 [cited 2013 May 21];29(45):7878–82. Available from: http://dx.doi.org/10.1016/j.vaccine.2011.08.069

59. Lei T, Siu K-L, Kok K-H, Chan K-H, Chan EYT, Hung IFN, et al. Anti-ganglioside antibodies were not detected in human subjects infected with or vaccinated against 2009 pandemic influenza A (H1N1) virus. Vaccine [Internet]. 2012 Mar 30 [cited 2013 May 29];30(16):2605–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22342549

60. Oski FA, Naiman JL. Effect of Live Measles Vaccine on the Platelet Count — NEJM [Internet]. [cited 2013 May 21]. Available from: http://www.nejm.org/doi/full/10.1056/NEJM196608182750703

61. Miller E, Waight P, Farrington CP, Andrews N, Stowe J, Taylor B. Idiopathic thrombocytopenic purpura and MMR vaccine. Archives of disease in childhood [Internet]. 2001 Mar [cited 2013 May 21];84(3):227–9. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1718684&tool=pmcentrez&rendertype=abstract

62. Andrews N, Stowe J, Miller E, Svanström H, Johansen K, Bonhoeffer J, et al. A collaborative approach to investigating the risk of thrombocytopenic purpura after measles-mumps-rubella vaccination in England and Denmark. Vaccine [Internet]. 2012 Apr 19 [cited 2013 May 21];30(19):3042–6. Available from: http://dx.doi.org/10.1016/j.vaccine.2011.06.009

63. Black C, Kaye JA, Jick H. MMR vaccine and idiopathic thrombocytopaenic purpura. British journal of clinical pharmacology [Internet]. 2003 Jan [cited 2013 May 21];55(1):107–11. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1884189&tool=pmcentrez&rendertype=abstract

64. Böttiger M, Christenson B, Romanus V, Taranger J, Strandell A. Swedish experience of two dose vaccination programme aiming at eliminating measles, mumps, and rubella. British medical journal (Clinical research ed.) [Internet]. 1987 Nov 14 [cited 2013 May 21];295(6608):1264–7. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1248321&tool=pmcentrez&rendertype=abstract

65. Stowe J, Kafatos G, Andrews N, Miller E. Idiopathic thrombocytopenic purpura and the second dose of MMR. Archives of disease in childhood [Internet]. 2008 Feb 1 [cited 2013 May 21];93(2):182–3. Available from: http://adc.bmj.com/content/93/2/182.long

66. Courrier A, Simonnet P, Lopez D, Scherer C, Stenbach G, Rumilly P, et al. PERIPHERAL NEUROPATHY FOLLOWING FETAL BOVINE CELL RABIES VACCINE. The Lancet [Internet]. 1986 May [cited 2013 May 21];327(8492):1273. Available from: http://dx.doi.org/10.1016/S0140-6736(86)91410-8

67. Siddiqui A, Usmani RI, Anwer S, Afsar S. Guillain-Barre syndrome occurring after rabies vaccination. JPMA. The Journal of the Pakistan Medical Association [Internet]. 2005 Feb [cited 2013 May 21];55(2):87–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15813639

68. Knittel T, Ramadori G, Mayet W-J, Löhr H, Meyer Zum Büschenfelde K-H. GUILLAIN-BARRÉSYNDROME AND HUMAN DIPLOID CELL RABIES VACCINE. The Lancet [Internet]. 1989 Jun [cited 2013 May 21];333(8650):1334–5. Available from: http://dx.doi.org/10.1016/S0140-6736(89)92734-7

69. Israeli E, Agmon-Levin N, Blank M, Shoenfeld Y. Adjuvants and autoimmunity. Lupus [Internet]. 2009 Nov [cited 2013 May 21];18(13):1217–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19880572

70. WHO | Questions and Answers about macrophagic myofasciitis (MMF). World Health Organization; [cited 2013 May 21]; Available from: http://www.who.int/vaccine_safety/committee/topics/aluminium/questions/en/

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

72. Galli L, Chiappini E, De Martino M. Infections and autoimmunity. The Pediatric infectious disease journal [Internet]. 2012 Dec [cited 2013 May 29];31(12):1295–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23188099

73. Poland GA, Jacobsen SJ. Influenza vaccine, Guillain-Barré syndrome, and chasing zero. Vaccine [Internet]. 2012 Aug 31 [cited 2013 May 22];30(40):5801–3. Available from: http://dx.doi.org/10.1016/j.vaccine.2012.06.093

74. McCarthy N, Giesecke J. Incidence of Guillain-Barré syndrome following infection with Campylobacter jejuni. American journal of epidemiology [Internet]. 2001 Mar 15 [cited 2013 May 21];153(6):610–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11257070

75. Tam CC, Rodrigues LC, Petersen I, Islam A, Hayward A, O'Brien SJ. Incidence of Guillain-Barré syndrome among patients with Campylobacter infection: a general practice research database study. The Journal of infectious diseases [Internet]. 2006 Jul 1 [cited 2013 May 21];194(1):95–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16741887

76. Carapetis JR, Currie BJ, Good MF. Towards understanding the pathogenesis of rheumatic fever. Scandinavian journal of rheumatology [Internet]. 1996 Jan [cited 2013 May 29];25(3):127–31; discussion 132–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8668953

77. Eison TM, Ault BH, Jones DP, Chesney RW, Wyatt RJ. Post-streptococcal acute glomerulonephritis in children: clinical features and pathogenesis. Pediatric nephrology (Berlin, Germany) [Internet]. 2011 Mar [cited 2013 May 29];26(2):165–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20652330

78. Kindermann I, Barth C, Mahfoud F, Ukena C, Lenski M, Yilmaz A, et al. Update on Myocarditis. Journal of the American College of Cardiology [Internet]. 2012 Feb [cited 2013 May 21];59(9):779–92. Available from: http://dx.doi.org/10.1016/j.jacc.2011.09.074

79. Mayer JL, Beardsley DS. Varicella-associated thrombocytopenia: autoantibodies against platelet surface glycoprotein V. Pediatric research [Internet]. 1996 Oct [cited 2013 May 29];40(4):615–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8888292

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

80. Wraith DC, Goldman M, Lambert P-H. Vaccination and autoimmune disease: what is the evidence? Lancet [Internet]. 2003 Nov 15 [cited 2012 Nov 9];362(9396):1659–66. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14630450

81. Salemi S, D'Amelio R. Are anti-infectious vaccinations safe and effective in patients with autoimmunity? International reviews of immunology [Internet]. Informa UK Ltd London, UK; 2010 Jun 3 [cited 2012 Nov 9];29(3):270–314. Available from: http://informahealthcare.com/doi/abs/10.3109/08830185.2010.483028

82. van Assen S, Elkayam O, Agmon-Levin N, Cervera R, Doran MF, Dougados M, et al. Vaccination in adult patients with auto-immune inflammatory rheumatic diseases: a systematic literature review for the European League Against Rheumatism evidence-based recommendations for vaccination in adult patients with auto-immune inflammatory rheuma. Autoimmun Rev [Internet]. 2010/12/25 ed. 2011;10(6):341–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21182987

83. Rahier J-F, Moutschen M, Van Gompel A, Van Ranst M, Louis E, Segaert S, et al. Vaccinations in patients with immune-mediated inflammatory diseases. Rheumatology (Oxford, England) [Internet]. 2010 Oct [cited 2012 Nov 9];49(10):1815–27. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2936949&tool=pmcentrez&rendertype=abstract

84. Chalmers A, Scheifele D, Patterson C, Williams D, Weber J, Shuckett R, et al. Immunization of patients with rheumatoid arthritis against influenza: a study of vaccine safety and immunogenicity. J Rheumatol [Internet]. 1994/07/01 ed. 1994;21(7):1203–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7966058

85. Del Porto F, Lagana B, Biselli R, Donatelli I, Campitelli L, Nisini R, et al. Influenza vaccine administration in patients with systemic lupus erythematosus and rheumatoid arthritis. Safety and immunogenicity. Vaccine [Internet]. 2006/02/10 ed. 2006;24(16):3217–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16466833

86. Denman EJ, Denman AM, Greenwood BM, Gall D, Heath RB. Failure of cytotoxic drugs to suppress immune responses of patients with rheumatoid arthritis. Ann Rheum Dis [Internet]. 1970/05/01 ed. 1970;29(3):220–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/4194200

87. Fomin I, Caspi D, Levy V, Varsano N, Shalev Y, Paran D, et al. Vaccination against influenza in rheumatoid arthritis: the effect of disease modifying drugs, including TNF alpha blockers. Ann Rheum Dis [Internet]. 2005/07/15 ed. 2006;65(2):191–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16014674

88. Elkayam O, Bashkin A, Mandelboim M, Litinsky I, Comaheshter D, Levartovsky D, et al. The effect of infliximab and timing of vaccination on the humoral response to influenza vaccination in patients with rheumatoid arthritis and ankylosing spondylitis. Semin Arthritis Rheum [Internet]. 2009/02/28 ed. 2010;39(6):442–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19246078

89. Gelinck LB, van der Bijl AE, Beyer WE, Visser LG, Huizinga TW, van Hogezand RA, et al. The effect of anti-tumour necrosis factor alpha treatment on the antibody response to influenza vaccination. Ann Rheum Dis [Internet]. 2007/10/30 ed. 2008;67(5):713–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17965123

90. Oren S, Mandelboim M, Braun-Moscovici Y, Paran D, Ablin J, Litinsky I, et al. Vaccination against influenza in patients with rheumatoid arthritis: the effect of rituximab on the humoral response. Ann Rheum Dis [Internet]. 2007/11/06 ed. 2008;67(7):937–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17981914

91. Kaine JL, Kivitz AJ, Birbara C, Luo AY. Immune responses following administration of influenza and pneumococcal vaccines to patients with rheumatoid arthritis receiving adalimumab. J Rheumatol [Internet]. 2007/02/17 ed. 2007;34(2):272–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17304653

92. Mori S, Ueki Y, Hirakata N, Oribe M, Hidaka T, Oishi K. Impact of tocilizumab therapy on antibody response to influenza vaccine in patients with rheumatoid arthritis. Ann Rheum Dis [Internet]. 2012/08/14 ed. 2012; Available from: http://www.ncbi.nlm.nih.gov/pubmed/22887851

93. Kobie JJ, Zheng B, Bryk P, Barnes M, Ritchlin CT, Tabechian DA, et al. Decreased influenza-specific B cell responses in rheumatoid arthritis patients treated with anti-tumor necrosis factor. Arthritis Res Ther [Internet]. 2011/12/20 ed. 2011;13(6):R209. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22177419

94. Kubota T, Nii T, Nanki T, Kohsaka H, Harigai M, Komano Y, et al. Anti-tumor necrosis factor therapy does not diminish the immune response to influenza vaccine in Japanese patients with rheumatoid arthritis. 2007/12/18 ed. 2007;17(6):531–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18084712

95. Nii T, Kubota T, Nanki T, Komano Y, Harigai M, Kohsaka H, et al. Reevaluation of antibody titers 1 year after influenza vaccination in patients with rheumatoid arthritis receiving TNF blockers. 2008/11/19 ed. 2009;19(2):216–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19015815

96. Kapetanovic MC, Saxne T, Nilsson JA, Geborek P. Influenza vaccination as model for testing immune modulation induced by anti-TNF and methotrexate therapy in rheumatoid arthritis patients. Rheumatology (Oxford) [Internet]. 2006/11/23 ed. 2007;46(4):608–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17114801

97. Kivitz, Joy Schechtman, Michele Texter A, Chartash. F and E. Assessment of Immune Responses to Pneumococcal and Influenza Vaccines in Patients with Rheumatoid Arthritis Receiving CertolizumabPegol. ArthritisRheum 63(10-2.Suppl.) pS488 ACRMeetings Chicago,USA abstract. 2011.

98. Gelinck LB, Teng YK, Rimmelzwaan GF, van den Bemt BJ, Kroon FP, van Laar JM. Poor serological responses upon influenza vaccination in patients with rheumatoid arthritis treated with rituximab. Ann Rheum Dis [Internet]. 2007/09/21 ed. 2007;66(10):1402–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17881666

99. van Assen S, Holvast A, Benne CA, Posthumus MD, van Leeuwen MA, Voskuyl AE, et al. Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. Arthritis Rheum [Internet]. 2009/12/30 ed. 2010;62(1):75–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20039396

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 inspite of 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 responses to H1N1 vaccination.

References

100. Adler S, Krivine A, Weix J, Rozenberg F, Launay O, Huesler J, et al. Protective effect of A/H1N1 vaccination in immune-mediated disease--a prospectively controlled vaccination study. Rheumatology (Oxford) [Internet]. 2011/12/16 ed. 2012;51(4):695–700. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22171015

101. Gabay C, Bel M, Combescure C, Ribi C, Meier S, Posfay-Barbe K, et al. Impact of synthetic and biologic disease-modifying antirheumatic drugs on antibody responses to the AS03-adjuvanted pandemic influenza vaccine: a prospective, open-label, parallel-cohort, single-center study. Arthritis Rheum [Internet]. 2011/03/09 ed. 2011;63(6):1486–96. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21384334

102. Iwamoto M, Homma S, Onishi S, Kamata Y, Nagatani K, Yamagata Z, et al. Low level of seroconversion after a novel influenza A/H1N1/2009 vaccination in Japanese patients with rheumatoid arthritis in the 2009 season. Rheumatol Int [Internet]. 2011/09/02 ed. 2011; Available from:7http://www.ncbi.nlm.nih.gov/pubmed/21881985

103. Saad CG, Borba EF, Aikawa NE, Silva CA, Pereira RM, Calich AL, et al. Immunogenicity and safety of the 2009 non-adjuvanted influenza A/H1N1 vaccine in a large cohort of autoimmune rheumatic diseases. Ann Rheum Dis [Internet]. 2011/05/05 ed. 2011;70(6):1068–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21540203

104. Ribeiro AC, Guedes LK, Moraes JC, Saad CG, Aikawa NE, Calich AL, et al. Reduced seroprotection after pandemic H1N1 influenza adjuvant-free vaccination in patients with rheumatoid arthritis: implications for clinical practice. Ann Rheum Dis [Internet]. 2011/08/24 ed. 2011;70(12):2144–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21859696

105. França ILA, Ribeiro ACM, Aikawa NE, Saad CGS, Moraes JCB, Goldstein-Schainberg C, et al. TNF blockers show distinct patterns of immune response to the pandemic influenza A H1N1 vaccine in inflammatory arthritis patients.

Rheumatology (Oxford, England) [Internet]. 2012 Nov [cited 2012 Nov 9];51(11):2091–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22908326

106. Ribeiro AC, Laurindo IM, Guedes LK, Saad CG, Moraes JC, Silva CA, et al. Abatacept severely reduces the immune response to pandemic 2009 influenza A/H1N1 vaccination in patients with rheumatoid arthritis. Arthritis care & research [Internet]. 2012 Sep 4 [cited 2012 Dec 12]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/22949223

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

91. Kaine JL, Kivitz AJ, Birbara C, Luo AY. Immune responses following administration of influenza and pneumococcal vaccines to patients with rheumatoid arthritis receiving adalimumab. J Rheumatol [Internet]. 2007/02/17 ed. 2007;34(2):272–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17304653

107. Bingham 3rd CO, Looney RJ, Deodhar A, Halsey N, Greenwald M, Codding C, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. Arthritis Rheum [Internet]. 2009/12/30 ed. 2010;62(1):64–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20039397

108. Elkayam O, Ablin J, Caspi D. Safety and efficacy of vaccination against streptococcus pneumonia in patients with rheumatic diseases. Autoimmun Rev [Internet]. 2007/04/07 ed. 2007;6(5):312–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17412304

109. Elkayam O, Paran D, Caspi D, Litinsky I, Yaron M, Charboneau D, et al. Immunogenicity and safety of pneumococcal vaccination in patients with rheumatoid arthritis or systemic lupus erythematosus. Clin Infect Dis [Internet]. 2001/12/12 ed. 2002;34(2):147–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11740700

110. Kapetanovic MC, Saxne T, Sjoholm A, Truedsson L, Jonsson G, Geborek P. Influence of methotrexate, TNF blockers and prednisolone on antibody responses to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis. Rheumatology (Oxford) [Internet]. 2005/11/17 ed. 2006;45(1):106–11.

111. Visvanathan S, Keenan GF, Baker DG, Levinson AI, Wagner CL. Response to pneumococcal vaccine in patients with early rheumatoid arthritis receiving infliximab plus methotrexate or methotrexate alone. J Rheumatol [Internet]. 2007/04/21 ed. 2007;34(5):952–7.

112. Kapetanovic MC, Roseman C, Jonsson G, Truedsson L, Saxne T, Geborek P. Antibody response is reduced following vaccination with 7-valent conjugate pneumococcal vaccine in adult methotrexate-treated patients with established arthritis, but not those treated with tumor necrosis factor inhibitors. Arthritis Rheum [Internet]. 2011/08/13 ed. 2011;63(12):3723–32.

113. Kapetanovic MC, Roseman C, Jonsson G, Truedsson L. Heptavalent pneumococcal conjugate vaccine elicits similar antibody response as standard 23-valent polysaccharide vaccine in adult patients with RA treated with immunomodulating drugs. Clin Rheumatol [Internet]. 2011/10/01 ed. 2011;30(12):1555–61.

114. Elkayam O, Caspi D, Reitblatt T, Charboneau D, Rubins JB. The effect of tumor necrosis factor blockade on the response to pneumococcal vaccination in patients with rheumatoid arthritis and ankylosing spondylitis. Semin Arthritis Rheum [Internet]. 2004/02/24 ed. 2004;33(4):283–8.

115. Gelinck LB, van der Bijl AE, Visser LG, Huizinga TW, van Hogezand RA, Rijkers GT, et al. Synergistic immunosuppressive effect of anti-TNF combined with methotrexate on antibody responses to the 23 valent pneumococcal polysaccharide vaccine. Vaccine [Internet]. 2008/05/27 ed. 2008;26(27-28):3528–33.

116. Tay L, Leon F, Vratsanos G, Raymond R, Corbo M. Vaccination response to tetanus toxoid and 23-valent pneumococcal vaccines following administration of a single dose of abatacept: a randomized, open-label, parallel group study in healthy subjects. Arthritis research & therapy [Internet]. 2007 Jan

117. Schiff M, Kaell A, Vratsanos G BK. Response to pneumococcal vaccine in rheumatoid arthritis patients with an inadequate response to anti-TNF therapy treated with abatacept in the ARRIVE trial. Ann Rheum Dis. 2007;66 (S11):437.

118. Mori S, Ueki Y, Akeda Y, Hirakata N, Oribe M, Shiohira Y, et al. Pneumococcal polysaccharide vaccination in rheumatoid arthritis patients receiving tocilizumab therapy. Annals of the rheumatic diseases [Internet]. 2013 Jan 23 [cited 2013 Apr 10]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/23345600

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

86. Denman EJ, Denman AM, Greenwood BM, Gall D, Heath RB. Failure of cytotoxic drugs to suppress immune responses of patients with rheumatoid arthritis. Ann Rheum Dis [Internet]. 1970/05/01 ed. 1970;29(3):220–31. Available from:

107. Bingham 3rd CO, Looney RJ, Deodhar A, Halsey N, Greenwald M, Codding C, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. Arthritis Rheum [Internet]. 2009/12/30 ed. 2010;62(1):64–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20039397

116. Tay L, Leon F, Vratsanos G, Raymond R, Corbo M. Vaccination response to tetanus toxoid and 23-valent pneumococcal vaccines following administration of a single dose of abatacept: a randomized, open-label, parallel group study in healthy subjects. Arthritis research & therapy [Internet]. 2007 Jan [cited 2012 Nov 9];9(2):R38. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1906816&tool=pmcentrez&rendertype=abstract

119. Devey ME, Bleasdale K, Isenberg DA. Antibody affinity and IgG subclass of responses to tetanus toxoid in patients with rheumatoid arthritis and systemic lupus erythematosus. Clin Exp Immunol [Internet]. 1987/06/01 ed. 1987;68(3):562–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3652524

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

120. Elkayam O, Yaron M, Caspi D. Safety and efficacy of vaccination against hepatitis B in patients with rheumatoid arthritis. Ann Rheum Dis [Internet]. 2002/06/25 ed. 2002;61(7):623–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12079904

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

121. Erguven M, Kaya B, Hamzah OY, Tufan F. Evaluation of immune response to hepatitis A vaccination and vaccine safety in juvenile idiopathic arthritis. Journal of the Chinese Medical Association : JCMA [Internet]. 2011 May [cited 2012 Nov 9];74(5):205–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21550006

122. ter Waarbeek H, Dukers-Muijrers N, Hoebe C, editors. A Study of the Effectiveness of Hepatitis A Vaccination in Travelers with Immunosuppressive Medication. 11th Conference of the International Society of Travel Medicine; 2009; Budapest, Hungary.

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 agents (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/m^2/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

123. Heijstek MW, Pileggi GCS, Zonneveld-Huijssoon E, Armbrust W, Hoppenreijs EPAH, Uiterwaal CSPM, et al. Safety of measles, mumps and rubella vaccination in juvenile idiopathic arthritis. Annals of the rheumatic diseases [Internet]. 2007 Oct [cited 2012 Nov 11];66(10):1384–7. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1994321&tool=pmcentrez&rendertype=abstract

124. Borte S, Liebert UG, Borte M, Sack U. Efficacy of measles, mumps and rubella revaccination in children with juvenile idiopathic arthritis treated with methotrexate and etanercept. Rheumatology (Oxford, England) [Internet]. 2009 Feb [cited 2012 Nov 11];48(2):144–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19074187

125. Heijstek MW, Gorter S, Vries LD De, Smits GP, Gageldonk PG Van, Berbers GAM, et al. Effects of the Live Attenuated Measles-Mumps-Rubella Booster Vaccination With Juvenile Idiopathic Arthritis. JAMA. 2013 Jun 19;309(23):2449-56.

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 aditionally (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

126. Pileggi GS, de Souza CBS, Ferriani VPL. Safety and immunogenicity of varicella vaccine in patients with juvenile rheumatic diseases receiving methotrexate and corticosteroids. Arthritis care & research [Internet]. 2010 Jul [cited 2012 Nov 11];62(7):1034–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20235203

5.1.9 Herpes zoster vaccine

Out of 463'541 medicare beneficiaries (292'169 with RA, 89'565 psoriasis, 11'030 psoriatic arthritis, 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

127. Zhang J, Xie F, Delzell E, Chen L, Winthrop KL, Lewis JD, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. JAMA : the journal of the American Medical Association [Internet]. 2012 Jul 4 [cited 2012 Nov 12];308(1):43–9. Available from: http://jama.jamanetwork.com/article.aspx?articleid=1212306

128. Prevention of Herpes Zoster Recommendations of the Advisory Committee on Immunization Practices (ACIP) [Internet]. [cited 2012 Nov 12]. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5705a1.htm

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

129. Mota LM, Oliveira AC, Lima RA, Santos-Neto LL, Tauil PL. [Vaccination against yellow fever among patients on immunosuppressors with diagnoses of rheumatic diseases]. Rev Soc Bras Med Trop [Internet]. 2009/03/17 ed. 2009;42(1):23–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19287931

130. Scheinberg M, Guedes-Barbosa LS, Mangueira C, Rosseto EA, Mota L, Oliveira AC, et al. Yellow fever revaccination during infliximab therapy. Arthritis Care Res (Hoboken) [Internet]. 2010/06/11 ed. 2010;62(6):896–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20535801

131. Kernéis S, Launay O, Ancelle T, Iordache L, Naneix-Laroche V, Méchaï F, et al. Safety and immunogenicity of yellow fever 17D vaccine in adults receiving systemic corticosteroid therapy: An observational cohort study. Arthritis care & research [Internet]. 2013 Apr 1 [cited 2013 Jun 13]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/23554297

In patients with rheumatoid arthritis, there are no published data on vacccinations 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

85. Del Porto F, Lagana B, Biselli R, Donatelli I, Campitelli L, Nisini R, et al. Influenza vaccine administration in patients with systemic lupus erythematosus and rheumatoid arthritis. Safety and immunogenicity. Vaccine [Internet]. 2006/02/10 ed. 2006;24(16):3217–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16466833

132. Williams GW, Steinberg AD, Reinertsen JL, Klassen LW, Decker JL, Dolin R. Influenza immunization in systemic lupus eruthematosus. A double-blind trial. 1978/06/01 ed. 1978;88(6):729–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/352210

133. Brodman R, Gilfillan R, Glass D, Schur PH. Influenzal vaccine response in systemic lupus erythematosus. 1978/06/01 ed. 1978;88(6):735–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/307353

134. Ristow SC, Douglas RG, Condemi JJ. Influenza vaccination of patients with systemic lupus erythematosus. Annals of internal medicine [Internet]. 1978 Jun [cited 2012 Nov 11];88(6):786–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/666135

135. Mercado U, Acosta H, Avendano L. Influenza vaccination of patients with systemic lupus erythematosus. 2004/05/18 ed. 2004;56(1):16–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15144037

136. Holvast A, Huckriede A, Wilschut J, Horst G, De Vries JJ, Benne CA, et al. Safety and efficacy of influenza vaccination in systemic lupus erythematosus patients with quiescent disease. Ann Rheum Dis [Internet]. 2005/12/03 ed. 2006;65(7):913–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16322083

137. Wiesik-Szewczyk E, Romanowska M, Mielnik P, Chwalinska-Sadowska H, Brydak LB, Olesinska M, et al. Anti-influenza vaccination in systemic lupus erythematosus patients: an analysis of specific humoral response and vaccination safety. Clin Rheumatol [Internet]. 2010/02/09 ed. 2010;29(6):605–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20140692

138. Kostianovsky A, Charles P, Alves JF, Goulet M, Pagnoux C, Le Guern V, et al. Immunogenicity and safety of seasonal and 2009 pandemic A/H1N1 influenza vaccines for patients with autoimmune diseases: a prospective, monocentre trial on 199 patients. Clin Exp Rheumatol [Internet]. 2012/07/26 ed. 2012;30(1 Suppl 70):S83–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22640652

139. Setti M, Fenoglio D, Ansaldi F, Filaci G, Bacilieri S, Sticchi L, et al. Flu vaccination with a virosomal vaccine does not affect clinical course and immunological parameters in scleroderma patients. Vaccine [Internet]. 2009/02/10 ed. 2009;27(25-26):3367–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19200840

140. Crowe SR, Merrill JT, Vista ES, Dedeke AB, Thompson DM, Stewart S, et al. Influenza vaccination responses in human systemic lupus erythematosus: impact of clinical and demographic features. Arthritis and rheumatism [Internet]. 2011 Aug [cited 2012 Nov 11];63(8):2396–406. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3149742&tool=pmcentrez&rendertype=abstract

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

100. Adler S, Krivine A, Weix J, Rozenberg F, Launay O, Huesler J, et al. Protective effect of A/H1N1 vaccination in immune-mediated disease--a prospectively controlled vaccination study. Rheumatology (Oxford) [Internet]. 2011/12/16 ed. 2012;51(4):695–700. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22171015

101. Gabay C, Bel M, Combescure C, Ribi C, Meier S, Posfay-Barbe K, et al. Impact of synthetic and biologic disease-modifying antirheumatic drugs on antibody responses to the AS03-adjuvanted pandemic influenza vaccine: a prospective, open-label, parallel-cohort, single-center study. Arthritis Rheum [Internet]. 2011/03/09 ed. 2011;63(6):1486–96. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21384334

103. Saad CG, Borba EF, Aikawa NE, Silva CA, Pereira RM, Calich AL, et al. Immunogenicity and safety of the 2009 non-adjuvanted influenza A/H1N1 vaccine in a large cohort of autoimmune rheumatic diseases. Ann Rheum Dis [Internet]. 2011/05/05 ed. 2011;70(6):1068–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2154020

141. Urowitz MB, Anton A, Ibanez D, Gladman DD. Autoantibody response to adjuvant and nonadjuvant H1N1 vaccination in systemic lupus erythematosus. Arthritis care & research [Internet]. 2011 Nov [cited 2012 Nov 11];63(11):1517–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22034113

142. Borba EF, Saad CGS, Pasoto SG, Calich ALG, Aikawa NE, Ribeiro ACM, et al. Influenza A/H1N1 vaccination of patients with SLE: can antimalarial drugs restore diminished response under immunosuppressive therapy? Rheumatology (Oxford, England) [Internet]. 2012 Jun [cited 2012 Nov 11];51(6):1061–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22298793

143. Mathian A, Devilliers H, Krivine A, Costedoat-Chalumeau N, Haroche J, Huong DB-LT, et al. Factors influencing the efficacy of two injections of a pandemic 2009 influenza A (H1N1) nonadjuvanted vaccine in systemic lupus

erythematosus. Arthritis and rheumatism [Internet]. 2011 Nov [cited 2012 Nov 11];63(11):3502–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21811996

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

108. Elkayam O, Ablin J, Caspi D. Safety and efficacy of vaccination against streptococcus pneumonia in patients with rheumatic diseases. Autoimmun Rev [Internet]. 2007/04/07 ed. 2007;6(5):312–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17412304

109. Elkayam O, Paran D, Caspi D, Litinsky I, Yaron M, Charboneau D, et al. Immunogenicity and safety of pneumococcal vaccination in patients with rheumatoid arthritis or systemic lupus erythematosus. Clin Infect Dis [Internet]. 2001/12/12 ed. 2002;34(2):147–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11740700

116. Tay L, Leon F, Vratsanos G, Raymond R, Corbo M. Vaccination response to tetanus toxoid and 23-valent pneumococcal vaccines following administration of a single dose of abatacept: a randomized, open-label, parallel group study in healthy subjects. Arthritis research & therapy [Internet]. 2007 Jan [cited 2012 Nov 9];9(2):R38. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1906816&tool=pmcentrez&rendertype=abstract

144. Tarjan P, Sipka S, Marodi L, Nemes E, Lakos G, Gyimesi E, et al. No short-term immunological effects of Pneumococcus vaccination in patients with systemic lupus erythematosus. Scand J Rheumatol [Internet]. 2002/10/09 ed. 2002;31(4):211–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12369652

145. Battafarano DF, Battafarano NJ, Larsen L, Dyer PD, Older SA, Muehlbauer S, et al. Antigen-specific antibody responses in lupus patients following immunization. Arthritis Rheum [Internet]. 1998/10/20 ed. 1998;41(10):1828–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9778224

146. Jarrett MP, Schiffman G, Barland P, Grayzel AI. Impaired response to pneumococcal vaccine in systemic lupus erythematosus. Arthritis Rheum [Internet]. 1980/11/01 ed. 1980;23(11):1287–93. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7447963

147. Elkayam O, Paran D, Burke M, Zakut V, Ben-Yitshak R, Litinsky I, et al. Pneumococcal vaccination of patients with systemic lupus erythematosus: effects on generation of autoantibodies. Autoimmunity [Internet]. 2005 Nov [cited 2012 Nov 11];38(7):493–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16373254

148. Mercado U, Acosta H, Diaz-Molina R. Antibody response to pneumococcal polysaccharide vaccine in systemic sclerosis. J Rheumatol [Internet]. 2009/07/02 ed. 2009;36(7):1549–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19567636

149. Lipnick RN, Karsh J, Stahl NI, Blackwelder WC, Schiffman G, Klippel JH. Pneumococcal immunization in patients with systemic lupus erythematosus treated with immunosuppressives. J Rheumatol [Internet]. 1985/12/01 ed. 1985;12(6):1118–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/4093916

150. McDonald E, Jarrett MP, Schiffman G, Grayzel AI. Persistence of pneumococcal antibodies after immunization in patients with systemic lupus erythematosus. J Rheumatol [Internet]. 1984/06/01 ed. 1984;11(3):306–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6737372

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

116. Tay L, Leon F, Vratsanos G, Raymond R, Corbo M. Vaccination response to tetanus toxoid and 23-valent pneumococcal vaccines following administration of a single dose of abatacept: a randomized, open-label, parallel group study in healthy subjects. Arthritis research & therapy [Internet]. 2007 Jan [cited 2012 Nov 9];9(2):R38. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1906816&tool=pmcentrez&rendertype=abstract

119. Devey ME, Bleasdale K, Isenberg DA. Antibody affinity and IgG subclass of responses to tetanus toxoid in patients with rheumatoid arthritis and systemic lupus erythematosus. Clin Exp Immunol [Internet]. 1987/06/01 ed. 1987;68(3):562–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3652524

145. Battafarano DF, Battafarano NJ, Larsen L, Dyer PD, Older SA, Muehlbauer S, et al. Antigen-specific antibody responses in lupus patients following immunization. Arthritis Rheum [Internet]. 1998/10/20 ed. 1998;41(10):1828–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9778224

151. Nies K, Boyer R, Stevens R, Louie J. Anti-tetanus toxoid antibody synthesis after booster immunization in systemic lupus erythematosus. Comparison of the in vitro and in vivo responses. Arthritis Rheum [Internet]. 1980/12/01 ed. 1980;23(12):1343–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7006611

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 immunosuppressive 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

152. Kuruma KA, Borba EF, Lopes MH, de Carvalho JF, Bonfa E. Safety and efficacy of hepatitis B vaccine in systemic lupus erythematosus. Lupus [Internet]. 2007/06/20 ed. 2007;16(5):350–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17576737

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

145. Battafarano DF, Battafarano NJ, Larsen L, Dyer PD, Older SA, Muehlbauer S, et al. Antigen-specific antibody responses in lupus patients following immunization. Arthritis Rheum [Internet]. 1998/10/20 ed. 1998;41(10):1828–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9778224

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

153. Mok CC, Ho LY, Fong LS, To CH. Immunogenicity and safety of a quadrivalent human papillomavirus vaccine in patients with systemic lupus erythematosus: a case-control study. Annals of the rheumatic diseases [Internet]. 2012 May 15 [cited 2012 Nov 12]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/22589375

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, 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

128. Prevention of Herpes Zoster Recommendations of the Advisory Committee on Immunization Practices (ACIP) [Internet]. [cited 2012 Nov 12]. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5705a1.htm

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, 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 (see section 5).

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

Reference

129. Mota LM, Oliveira AC, Lima RA, Santos-Neto LL, Tauil PL. [Vaccination against yellow fever among patients on immunosuppressors with diagnoses of rheumatic diseases]. Rev Soc Bras Med Trop [Internet]. 2009/03/17 ed. 2009;42(1):23–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19287931

In patients with connective tissue diseases, there are no published data on vacccinations 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

89. Gelinck LB, van der Bijl AE, Beyer WE, Visser LG, Huizinga TW, van Hogezand RA, et al. The effect of anti-tumour necrosis factor alpha treatment on the antibody response to influenza vaccination. Ann Rheum Dis [Internet]. 2007/10/30 ed. 2008;67(5):713–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17965123

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

100. Adler S, Krivine A, Weix J, Rozenberg F, Launay O, Huesler J, et al. Protective effect of A/H1N1 vaccination in immune-mediated disease--a prospectively controlled vaccination study. Rheumatology (Oxford) [Internet]. 2011/12/16 ed. 2012;51(4):695–700. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22171015

101. Gabay C, Bel M, Combescure C, Ribi C, Meier S, Posfay-Barbe K, et al. Impact of synthetic and biologic disease-modifying antirheumatic drugs on antibody responses to the AS03-adjuvanted pandemic influenza vaccine: a prospective, open-label, parallel-cohort, single-center study. Arthritis Rheum [Internet]. 2011/03/09 ed. 2011;63(6):1486–96. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21384334

103. Saad CG, Borba EF, Aikawa NE, Silva CA, Pereira RM, Calich AL, et al. Immunogenicity and safety of the 2009 non-adjuvanted influenza A/H1N1 vaccine in a large cohort of autoimmune rheumatic diseases. Ann Rheum Dis [Internet]. 2011/05/05 ed. 2011;70(6):1068–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21540203

105. França ILA, Ribeiro ACM, Aikawa NE, Saad CGS, Moraes JCB, Goldstein-Schainberg C, et al. TNF blockers show distinct patterns of immune response to the pandemic influenza A H1N1 vaccine in inflammatory arthritis patients. Rheumatology (Oxford, England) [Internet]. 2012 Nov [cited 2012 Nov 9];51(11):2091–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22908326

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 responses 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

112. Kapetanovic MC, Roseman C, Jonsson G, Truedsson L, Saxne T, Geborek P. Antibody response is reduced following vaccination with 7-valent conjugate pneumococcal vaccine in adult methotrexate-treated patients with established arthritis, but not those treated with tumor necrosis factor inhibitors. Arthritis Rheum [Internet]. 2011/08/13 ed. 2011;63(12):3723–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21834061

114. Elkayam O, Caspi D, Reitblatt T, Charboneau D, Rubins JB. The effect of tumor necrosis factor blockade on the response to pneumococcal vaccination in patients with rheumatoid arthritis and ankylosing spondylitis. Semin Arthritis Rheum [Internet]. 2004/02/24 ed. 2004;33(4):283–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14978666

116. Tay L, Leon F, Vratsanos G, Raymond R, Corbo M. Vaccination response to tetanus toxoid and 23-valent pneumococcal vaccines following administration of a single dose of abatacept: a randomized, open-label, parallel group study in healthy subjects. Arthritis research & therapy [Internet]. 2007 Jan [cited 2012 Nov 9];9(2):

154. Mease PJ, Ritchlin CT, Martin RW, Gottlieb AB, Baumgartner SW, Burge DJ, et al. Pneumococcal vaccine response in psoriatic arthritis patients during treatment with etanercept. J Rheumatol [Internet]. 2004/07/02 ed. 2004;31(7):1356–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15229957

155. Roseman C, Truedsson L, Kapetanovic MC. The effect of smoking and alcohol consumption on markers of systemic inflammation, immunoglobulin levels and immune response following pneumococcal vaccination in patients with arthritis. Arthritis Res Ther [Internet]. 2012/07/25 ed. 2012;14(4):R170. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22824238

156. Salinas GF, De Rycke et al. L. TNF Alpha Impairs Humoral T Cell Dependent Antibody Responses. Philadelphia; 2009.

157. Franco Salinas G, De Rycke L, Barendregt B, Paramarta JE, Hreggvidstdottir H, Cantaert T, et al. Anti-TNF treatment blocks the induction of T cell-dependent humoral responses. Annals of the rheumatic diseases [Internet]. 2013 Jun [cited 2013 Jun 13];72(6):1037–43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22968102

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

156. Salinas GF, De Rycke et al. L. TNF Alpha Impairs Humoral T Cell Dependent Antibody Responses. Philadelphia; 2009.

157. Franco Salinas G, De Rycke L, Barendregt B, Paramarta JE, Hreggvidstdottir H, Cantaert T, et al. Anti-TNF treatment blocks the induction of T cell-dependent humoral responses. Annals of the rheumatic diseases [Internet]. 2013 Jun [cited 2013 Jun 13];72(6):1037–43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22968102

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

122. ter Waarbeek H, Dukers-Muijrers N, Hoebe C, editors. A Study of the Effectiveness of Hepatitis A Vaccination in Travelers with Immunosuppressive Medication. 11th Conference of the International Society of Travel Medicine; 2009; Budapest, Hungary.

5.3.6 Herpes zoster vaccine

Out of 463'541 medicare beneficiaries (292'169 with RA, 89'565 psoriasis, 11'030 psoriatic arthritis, 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

127. Zhang J, Xie F, Delzell E, Chen L, Winthrop KL, Lewis JD, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. JAMA : the journal of the American Medical Association [Internet]. 2012 Jul 4 [cited 2012 Nov 12];308(1):43–9. Available from: http://jama.jamanetwork.com/article.aspx?articleid=1212306

128. Prevention of Herpes Zoster Recommendations of the Advisory Committee on Immunization Practices (ACIP) [Internet]. [cited 2012 Nov 12]. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5705a1.htm

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

129. Mota LM, Oliveira AC, Lima RA, Santos-Neto LL, Tauil PL. [Vaccination against yellow fever among patients on immunosuppressors with diagnoses of rheumatic diseases]. Rev Soc Bras Med Trop [Internet]. 2009/03/17 ed. 2009;42(1):23–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1928793

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

158. Holvast A, Stegeman CA, Benne CA, Huckriede A, Wilschut JC, Palache AM, et al. Wegener's granulomatosis patients show an adequate antibody response to influenza vaccination. Ann Rheum Dis [Internet]. 2008/07/16 ed. 2009;68(6):873–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18625625

159. Zycinska K, Romanowska M, Nowak I, Rybicka K, Wardyn KA, Brydak LB. Antibody response to inactivated subunit influenza vaccine in patients with Wegener's granulomatosis. 2008/03/28 ed. 2007;58 Suppl 5(Pt 2):819–28. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18204196

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 (138). One study showed that H1N1 vaccination was immunogenic in patients with Takaysu arteriitis 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

100. Adler S, Krivine A, Weix J, Rozenberg F, Launay O, Huesler J, et al. Protective effect of A/H1N1 vaccination in immune-mediated disease--a prospectively controlled vaccination study. Rheumatology (Oxford) [Internet]. 2011/12/16 ed. 2012;51(4):695–700. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22171015

101. Gabay C, Bel M, Combescure C, Ribi C, Meier S, Posfay-Barbe K, et al. Impact of synthetic and biologic disease-modifying antirheumatic drugs on antibody responses to the AS03-adjuvanted pandemic influenza vaccine: a prospective, open-label, parallel-cohort, single-center study. Arthritis Rheum [Internet]. 2011/03/09 ed. 2011;63(6):1486–96. Available from:7http://www.ncbi.nlm.nih.gov/pubmed/21384334

103. Saad CG, Borba EF, Aikawa NE, Silva CA, Pereira RM, Calich AL, et al. Immunogenicity and safety of the 2009 non-adjuvanted influenza A/H1N1 vaccine in a large cohort of autoimmune rheumatic diseases. Ann Rheum Dis [Internet]. 2011/05/05 ed. 2011;70(6):1068–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21540203

138. Kostianovsky A, Charles P, Alves JF, Goulet M, Pagnoux C, Le Guern V, et al. Immunogenicity and safety of seasonal and 2009 pandemic A/H1N1 influenza vaccines for patients with autoimmune diseases: a prospective, monocentre trial on 199 patients. Clin Exp Rheumatol [Internet]. 2012/07/26 ed. 2012;30(1 Suppl 70):S83–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22640652

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

116. Tay L, Leon F, Vratsanos G, Raymond R, Corbo M. Vaccination response to tetanus toxoid and 23-valent pneumococcal vaccines following administration of a single dose of abatacept: a randomized, open-label, parallel group study in healthy subjects. Arthritis research & therapy [Internet]. 2007 Jan [cited 2012 Nov 9];9(2):R38. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1906816&tool=pmcentrez&rendertype=abstract

160. Hugle T, Bircher A, Walker UA. Streptococcal hypersensitivity reloaded: severe inflammatory syndrome in Behcet's disease following 23-valent polysaccharide Streptococcus pneumoniae vaccine. Rheumatology (Oxford) [Internet]. 2011/12/14 ed. 2012;51(4):761–2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22157598

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

161. Erkek E, Ayaslioglu E, Erkek AB, Kurtipek GS, Bagci Y. Response to vaccination against hepatitis B in patients with Behcet's disease. J Gastroenterol Hepatol [Internet]. 2005/09/22 ed. 2005;20(10):1508–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16174066

In patients with vasculitis, there are no published data on vacccinations 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

104. Ribeiro AC, Guedes LK, Moraes JC, Saad CG, Aikawa NE, Calich AL, et al. Reduced seroprotection after pandemic H1N1 influenza adjuvant-free vaccination in patients with rheumatoid arthritis: implications for clinical practice. Ann Rheum Dis [Internet]. 2011/08/24 ed. 2011;70(12):2144–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21859696

120. Elkayam O, Yaron M, Caspi D. Safety and efficacy of vaccination against hepatitis B in patients with rheumatoid arthritis. Ann Rheum Dis [Internet]. 2002/06/25 ed. 2002;61(7):623–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12079904

135. Mercado U, Acosta H, Avendano L. Influenza vaccination of patients with systemic lupus erythematosus. 2004/05/18 ed. 2004;56(1):16–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15144037

140. Crowe SR, Merrill JT, Vista ES, Dedeke AB, Thompson DM, Stewart S, et al. Influenza vaccination responses in human systemic lupus erythematosus: impact of clinical and demographic features. Arthritis and rheumatism [Internet]. 2011 Aug [cited 2012 Nov 11];63(8):2396–406. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3149742&tool=pmcentrez&rendertype=abstract

143. Mathian A, Devilliers H, Krivine A, Costedoat-Chalumeau N, Haroche J, Huong DB-LT, et al. Factors influencing the efficacy of two injections of a pandemic 2009 influenza A (H1N1) nonadjuvanted vaccine in systemic lupus erythematosus. Arthritis and rheumatism [Internet]. 2011 Nov [cited 2012 Nov 11];63(11):3502–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21811996

145. Battafarano DF, Battafarano NJ, Larsen L, Dyer PD, Older SA, Muehlbauer S, et al. Antigen-specific antibody responses in lupus patients following immunization. Arthritis Rheum [Internet]. 1998/10/20 ed. 1998;41(10):1828–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9778224

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

88. Elkayam O, Bashkin A, Mandelboim M, Litinsky I, Comaheshter D, Levartovsky D, et al. The effect of infliximab and timing of vaccination on the humoral response to influenza vaccination in patients with rheumatoid arthritis and ankylosing spondylitis. Semin Arthritis Rheum [Internet]. 2009/02/28 ed. 2010;39(6):442–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19246078

90. Oren S, Mandelboim M, Braun-Moscovici Y, Paran D, Ablin J, Litinsky I, et al. Vaccination against influenza in patients with rheumatoid arthritis: the effect of rituximab on the humoral response. Ann Rheum Dis [Internet]. 2007/11/06 ed. 2008;67(7):937–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17981914

98. Gelinck LB, Teng YK, Rimmelzwaan GF, Van den Bemt BJ, Kroon FP, Van Laar JM. Poor serological responses upon influenza vaccination in patients with rheumatoid arthritis treated with rituximab. Ann Rheum Dis [Internet]. 2007/09/21 ed. 2007;66(10):1402–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17881666

99. Van Assen S, Holvast A, Benne CA, Posthumus MD, Van Leeuwen MA, Voskuyl AE, et al. Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. Arthritis Rheum [Internet]. 2009/12/30 ed. 2010;62(1):75–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20039396

101. Gabay C, Bel M, Combescure C, Ribi C, Meier S, Posfay-Barbe K, et al. Impact of synthetic and biologic disease-modifying antirheumatic drugs on antibody responses to the AS03-adjuvanted pandemic influenza vaccine: a prospective, open-label, parallel-cohort, single-center study. Arthritis Rheum [Internet]. 2011/03/09 ed. 2011;63(6):1486–96. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21384334

107. Bingham 3rd CO, Looney RJ, Deodhar A, Halsey N, Greenwald M, Codding C, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. Arthritis Rheum [Internet]. 2009/12/30 ed. 2010;62(1):64–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20039397

116. Tay L, Leon F, Vratsanos G, Raymond R, Corbo M. Vaccination response to tetanus toxoid and 23-valent pneumococcal vaccines following administration of a single dose of abatacept: a randomized, open-label, parallel group study in healthy subjects. Arthritis research & therapy [Internet]. 2007 Jan [cited 2012 Nov 9];9(2):R38. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1906816&tool=pmcentrez&rendertype=abstract

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

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

* 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

125. Heijstek MW, Gorter S, Vries LD De, Smits GP, Gageldonk PG Van, Berbers GAM, et al. Effects of the Live Attenuated Measles-Mumps-Rubella Booster Vaccination With Juvenile Idiopathic Arthritis. JAMA. 2013 Jun 19;309(23):2449-56.

128. Prevention of Herpes Zoster Recommendations of the Advisory Committee on Immunization Practices (ACIP) [Internet]. [cited 2012 Nov 12]. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5705a1.htm

162. Visser LG. The immunosuppressed traveler. Infectious disease clinics of North America [Internet]. 2012 Sep [cited 2013 Apr 10];26(3):609–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22963773

163. Schweizerische Gesellschaft für Rheumatologie. Impfempfehlungen für Patienten mit entzündlich-rheumatischen Erkrankungen [Internet]. 2010. Available from: http://www.rheuma-net.ch/Richtlinien

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 H1N1vaccination, 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

101. Gabay C, Bel M, Combescure C, Ribi C, Meier S, Posfay-Barbe K, et al. Impact of synthetic and biologic disease-modifying antirheumatic drugs on antibody responses to the AS03-adjuvanted pandemic influenza vaccine: a prospective, open-label, parallel-cohort, single-center study. Arthritis Rheum [Internet]. 2011/03/09 ed. 2011;63(6):1486–96. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21384334

102. Iwamoto M, Homma S, Onishi S, Kamata Y, Nagatani K, Yamagata Z, et al. Low level of seroconversion after a novel influenza A/H1N1/2009 vaccination in Japanese patients with rheumatoid arthritis in the 2009 season. Rheumatol Int [Internet]. 2011/09/02 ed. 2011; Available from: http://www.ncbi.nlm.nih.gov/pubmed/21881985

143. Mathian A, Devilliers H, Krivine A, Costedoat-Chalumeau N, Haroche J, Huong DB-LT, et al. Factors influencing the efficacy of two injections of a pandemic 2009 influenza A (H1N1) nonadjuvanted vaccine in systemic lupus erythematosus. Arthritis and rheumatism [Internet]. 2011 Nov [cited 2012 Nov 11];63(11):3502–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21811996

152. Kuruma KA, Borba EF, Lopes MH, De Carvalho JF, Bonfa E. Safety and efficacy of hepatitis B vaccine in systemic lupus erythematosus. Lupus [Internet]. 2007/06/20 ed. 2007;16(5):350–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17576737

161. Erkek E, Ayaslioglu E, Erkek AB, Kurtipek GS, Bagci Y. Response to vaccination against hepatitis B in patients with Behcet's disease. J Gastroenterol Hepatol [Internet]. 2005/09/22 ed. 2005;20(10):1508–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16174066

9 All references

1. Bijl M, Kallenberg CG, Van Assen S. Vaccination of the immune-compromised patients with focus on patients with autoimmune-inflammatory diseases. Neth J Med. 2011/02/18 ed. 2011;69(1):5–13.

2. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum. 2002/10/02 ed. 2002;46(9):2287–93.

3. Wagner UG, Koetz K, Weyand CM, Goronzy JJ. Perturbation of the T cell repertoire in rheumatoid arthritis. Proceedings of the National Academy of Sciences of the United States of America. 1998 Nov 24;95(24):14447–52.

4. Koetz K, Bryl E, Spickschen K, O'Fallon WM, Goronzy JJ, Weyand CM. T cell homeostasis in patients with rheumatoid arthritis. Proceedings of the National Academy of Sciences of the United States of America. 2000 Aug 1;97(16):9203–8.

5. Peter H-H, Pichler WJ, Müller-Ladner U. Klinische Immunologie. Urban & Fischer Bei Elsev; 2012.

6. Bernatsky S, Hudson M, Suissa S. Anti-rheumatic drug use and risk of serious infections in rheumatoid arthritis. Rheumatology (Oxford). 2007/05/05 ed. 2007;46(7):1157–60.

7. Gluck T, Kiefmann B, Grohmann M, Falk W, Straub RH, Scholmerich J. Immune status and risk for infection in patients receiving chronic immunosuppressive therapy. J Rheumatol. 2005/08/04 ed. 2005;32(8):1473–80.

8. Salliot C, Gossec L, Ruyssen-Witrand A, Luc M, Duclos M, Guignard S, et al. Infections during tumour necrosis factor-alpha blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients. Rheumatology (Oxford). 2006/08/02 ed. 2007;46(2):327–34.

9. Curtis JR, Patkar N, Xie A, Martin C, Allison JJ, Saag M, et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum. 2007/03/30 ed. 2007;56(4):1125–33.

10. Listing J, Strangfeld A, Kary S, Rau R, Von Hinueber U, Stoyanova-Scholz M, et al. Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum. 2005/10/29 ed. 2005;52(11):3403–12.

11. Bernatsky S, Habel Y, Rahme E. Observational studies of infections in rheumatoid arthritis: a metaanalysis of tumor necrosis factor antagonists. J Rheumatol. 2010/04/03 ed. 2010;37(5):928–31.

12. Salmon-Ceron D, Tubach F, Lortholary O, Chosidow O, Bretagne S, Nicolas N, et al. Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. Ann Rheum Dis. 2010/12/24 ed. 2011;70(4):616–23.

13. Curtis JR, Xie F, Chen L, Baddley JW, Beukelman T, Saag KG, et al. The comparative risk of serious infections among rheumatoid arthritis patients starting or switching biological agents. Ann Rheum Dis. 2011/05/19 ed. 2011;70(8):1401–6.

14. Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. Ann Rheum Dis. 2008/01/22 ed. 2009;68(1):25–32.

15. Singh J, Wells G, Christensen R, Tanjong Ghogomu E, Maxwell L, Jk M, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview (Review). Cochrane Database Syst Rev. 2011 Feb 16;(2):CD008794.

16. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine. 2003 Sep;82(5):299–308.

17. Ruangjutipopan S, Kasitanon N, Louthrenoo W, Sukitawut W, Wichainun R. Causes of death and poor survival prognostic factors in thai patients with systemic sclerosis. Journal of the Medical Association of Thailand = Chotmaihet thangphaet. 2002 Nov;85(11):1204–9.

18. Blumentals WA, Arreglado A, Napalkov P, Toovey S. Rheumatoid arthritis and the incidence of influenza and influenza-related complications: a retrospective cohort study. BMC Musculoskelet Disord. 2012/08/29 ed. 2012;13(1):158.

19. Nichol KL, Wuorenma J, Von Sternberg T. Benefits of influenza vaccination for low-, intermediate-, and high-risk senior citizens. Arch Intern Med. 1998/09/17 ed. 1998;158(16):1769–76.

20. Hak E, Nordin J, Wei F, Mullooly J, Poblete S, Strikas R, et al. Influence of high-risk medical conditions on the effectiveness of influenza vaccination among elderly members of 3 large managed-care organizations. Clin Infect Dis. 2002/07/30 ed. 2002;35(4):370–7.

21. Dirven L, Huizinga T, Allaart C. Risk factors for reported influenza and influenza-like symptoms in patients with rheumatoid arthritis. Scand J Rheumatol. 2012/07/21 ed. 2012;

22. Wotton CJ, Goldacre MJ. Risk of invasive pneumococcal disease in people admitted to hospital with selected immune-mediated diseases: record linkage cohort analyses. Journal of epidemiology and community health. 2012 Dec 6;66(12):1177–81.

23. Choi HJ, Kim MY, Kim HO, Park YM. An atypical varicella exanthem associated with the use of infliximab. Int J Dermatol. 2006/08/17 ed. 2006;45(8):999–1000.

24. Vonkeman H, Ten Napel C, Rasker H, Van de Laar M. Disseminated primary varicella infection during infliximab treatment. J Rheumatol. 2004/12/01 ed. 2004;31(12):2517–8.

25. Lee DH, Kim HS, Song YW, Cho KH. Development of varicella during adalimumab therapy. J Eur Acad Dermatol Venereol. 2007/04/24 ed. 2007;21(5):687–8.

26. Wolfe F, Michaud K, Chakravarty EF. Rates and predictors of herpes zoster in patients with rheumatoid arthritis and non-inflammatory musculoskeletal disorders. Rheumatology (Oxford). 2006/09/28 ed. 2006;45(11):1370–5.

27. Strangfeld A, Listing J, Herzer P, Liebhaber A, Rockwitz K, Richter C, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. JAMA. 2009/02/20 ed. 2009;301(7):737–44.

28. Smitten AL, Choi HK, Hochberg MC, Suissa S, Simon TA, Testa MA, et al. The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. Arthritis Rheum. 2007/12/01 ed. 2007;57(8):1431–8.

29. Manzi S, Kuller LH, Kutzer J, Pazin GJ, Sinacore J, Medsger TA, et al. Herpes zoster in systemic lupus erythematosus. The Journal of rheumatology. 1995 Jul;22(7):1254–8.

30. Galloway JB, Mercer LK, Moseley A, Dixon WG, Ustianowski AP, Helbert M, et al. Risk of skin and soft tissue infections (including shingles) in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Annals of the rheumatic diseases. 2012 Apr 24;annrheumdis–2011–201108–.

31. García-Doval I, Pérez-Zafrilla B, Descalzo MA, Roselló R, Hernández MV, Gómez-Reino JJ, et al. Incidence and risk of hospitalisation due to shingles and chickenpox in patients with rheumatic diseases treated with TNF antagonists. Annals of the rheumatic diseases. 2010 Oct 1;69(10):1751–5.

32. Santana IU, Gomes Ado N, Lyrio LD, Rios Grassi MF, Santiago MB. Systemic lupus erythematosus, human papillomavirus infection, cervical pre-malignant and malignant lesions: a systematic review. Clin Rheumatol. 2010/11/13 ed. 2011;30(5):665–72.

33. Nath R, Mant C, Luxton J, Hughes G, Raju KS, Shepherd P, et al. High risk of human papillomavirus type 16 infections and of development of cervical squamous intraepithelial lesions in systemic lupus erythematosus patients. Arthritis and rheumatism. 2007 May 15;57(4):619–25.

34. Tam L-S, Chan PKS, Ho SC, Yu MMY, Yim S-F, Cheung T-H, et al. Natural history of cervical papilloma virus infection in systemic lupus erythematosus - a prospective cohort study. The Journal of rheumatology. 2010 Feb;37(2):330–40.

35. Tanaka E, Urata Y. Risk of hepatitis B reactivation in patients treated with tumor necrosis factor-alpha inhibitors. 2011/12/14 ed. 2012;42(4):333–9.

36. World Tourism Organization, (UNWTO). International tourism on track to hit one billion by end of 2012 [Internet]. [cited 2012 Nov 8]. Available from: http://media.unwto.org/en/press-release/2012-09-12/international-tourism-track-hit-one-billion-end-2012

37. Bundesamt für Statistik. Reisen der Schweizer Wohnbevölkerung. Neuchâtel, Switzerland; 2010.

38. Wieten RW, Leenstra T, Goorhuis A, Van Vugt M, Grobusch MP. Health risks of travelers with medical conditions--a retrospective analysis. Journal of travel medicine. 19(2):104–10.

39. Baaten GG, Geskus RB, Kint JA, Roukens AH, Sonder GJ, Van den Hoek A. Symptoms of infectious diseases in immunocompromised travelers: a prospective study with matched controls. J Travel Med. 2011/09/08 ed. 2011;18(5):318–26.

40. Seong SS, Choi CB, Woo JH, Bae KW, Joung CL, Uhm WS, et al. Incidence of tuberculosis in Korean patients with rheumatoid arthritis (RA): effects of RA itself and of tumor necrosis factor blockers. J Rheumatol. 2007/02/20 ed. 2007;34(4):706–11.

41. Brassard P, Lowe AM, Bernatsky S, Kezouh A, Suissa S. Rheumatoid arthritis, its treatments, and the risk of tuberculosis in Quebec, Canada. Arthritis Rheum. 2009/02/28 ed. 2009;61(3):300–4.

42. Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Coster L, et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. Arthritis Rheum. 2005/06/30 ed. 2005;52(7):1986–92.

43. Tam LS, Li EK, Wong SM, Szeto CC. Risk factors and clinical features for tuberculosis among patients with systemic lupus erythematosus in Hong Kong. Scand J Rheumatol. 2002/11/29 ed. 2002;31(5):296–300.

44. Yun JE, Lee SW, Kim TH, Jun JB, Jung S, Bae SC, et al. The incidence and clinical characteristics of Mycobacterium tuberculosis infection among systemic lupus erythematosus and rheumatoid arthritis patients in Korea. Clin Exp Rheumatol. 2002/06/08 ed. 2002;20(2):127–32.

45. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, Keenlyside RA, Ziegler DW, Retailliau HF, et al. Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976--1977. American journal of epidemiology. 1979 Aug;110(2):105–23.

46. Schonberger LB, Hurwitz ES, Katona P, Holman RC, Bregman DJ. Guillain-Barré syndrome: its epidemiology and associations with influenza vaccination. Annals of neurology. 1981 Jan;9 Suppl:31–8.

47. Salmon DA, Proschan M, Forshee R, Gargiullo P, Bleser W, Burwen DR, et al. Association between Guillain-Barré syndrome and influenza A (H1N1) 2009 monovalent inactivated vaccines in the USA: a meta-analysis. The Lancet. 2013 Mar 12;381(9876):1461–8.

48. Dieleman J, Romio S, Johansen K, Weibel D, Bonhoeffer J, Sturkenboom M. Guillain-Barre syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe. BMJ (Clinical research ed.). 2011 Jan;343:d3908.

49. DeStefano F, Vellozzi C, Schonberger LB, Chen RT. Safety of adjuvanted pandemic influenza A (H1N1) 2009 vaccines. BMJ (Clinical research ed.). 2011 Jan;343:d4159.

50. Greene SK, Rett M, Weintraub 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 Project, 2009-2010. American journal of epidemiology. 2012 Jun 1;175(11):1100–9.

51. Yih WK, Lee GM, Lieu TA, Ball R, Kulldorff M, Rett M, et al. Surveillance for adverse events following receipt of pandemic 2009 H1N1 vaccine in the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) System, 2009-2010. American journal of epidemiology. 2012 Jun 1;175(11):1120–8.

52. Vellozzi C, Broder KR, Haber P, Guh A, Nguyen M, Cano M, et al. Adverse events following influenza A (H1N1) 2009 monovalent vaccines reported to the Vaccine Adverse Event Reporting System, United States, October 1, 2009-January 31, 2010. Vaccine. 2010 Oct 21;28(45):7248–55.

53. Wise ME, Viray M, Sejvar JJ, Lewis P, Baughman AL, Connor W, et al. Guillain-Barre syndrome during the 2009-2010 H1N1 influenza vaccination campaign: population-based surveillance among 45 million Americans. American journal of epidemiology. 2012 Jun 1;175(11):1110–9.

54. Williams SE, Pahud BA, Vellozzi C, Donofrio PD, Dekker CL, Halsey N, et al. Causality assessment of serious neurologic adverse events following 2009 H1N1 vaccination. Vaccine. 2011 Oct 26;29(46):8302–8.

55. Tokars JI, Lewis P, DeStefano F, Wise M, Viray M, Morgan O, et al. The risk of Guillain-Barré syndrome associated with influenza A (H1N1) 2009 monovalent vaccine and 2009-2010 seasonal influenza vaccines: results from self-controlled analyses. Pharmacoepidemiology and drug safety. 2012 May;21(5):546–52.

56. Verity C, Stellitano L, Winstone AM, Andrews N, Stowe J, Miller E. Guillain-Barré syndrome and H1N1 influenza vaccine in UK children. Lancet. 2011 Oct 29;378(9802):1545–6.

57. Stowe J, Andrews N, Wise L, Miller E. Investigation of the temporal association of Guillain-Barre syndrome with influenza vaccine and influenzalike illness using the United Kingdom General Practice Research Database. American journal of epidemiology. 2009 Feb 1;169(3):382–8.

58. Andrews N, Stowe J, Al-Shahi Salman R, Miller E. Guillain-Barré syndrome and H1N1 (2009) pandemic influenza vaccination using an AS03 adjuvanted vaccine in the United Kingdom: self-controlled case series. Vaccine. 2011 Oct 19;29(45):7878–82.

59. Lei T, Siu K-L, Kok K-H, Chan K-H, Chan EYT, Hung IFN, et al. Anti-ganglioside antibodies were not detected in human subjects infected with or vaccinated against 2009 pandemic influenza A (H1N1) virus. Vaccine. 2012 Mar 30;30(16):2605–10.

60. Oski FA, Naiman JL. Effect of Live Measles Vaccine on the Platelet Count — NEJM [Internet]. [cited 2013 May 21]. Available from: http://www.nejm.org/doi/full/10.1056/NEJM196608182750703

61. Miller E, Waight P, Farrington CP, Andrews N, Stowe J, Taylor B. Idiopathic thrombocytopenic purpura and MMR vaccine. Archives of disease in childhood. 2001 Mar;84(3):227–9.

62. Andrews N, Stowe J, Miller E, Svanström H, Johansen K, Bonhoeffer J, et al. A collaborative approach to investigating the risk of thrombocytopenic purpura after measles-mumps-rubella vaccination in England and Denmark. Vaccine. 2012 Apr 19;30(19):3042–6.

63. Black C, Kaye JA, Jick H. MMR vaccine and idiopathic thrombocytopaenic purpura. British journal of clinical pharmacology. 2003 Jan;55(1):107–11.

64. Böttiger M, Christenson B, Romanus V, Taranger J, Strandell A. Swedish experience of two dose vaccination programme aiming at eliminating measles, mumps, and rubella. British medical journal (Clinical research ed.). 1987 Nov 14;295(6608):1264–7.

65. Stowe J, Kafatos G, Andrews N, Miller E. Idiopathic thrombocytopenic purpura and the second dose of MMR. Archives of disease in childhood. 2008 Feb 1;93(2):182–3.

66. Courrier A, Simonnet P, Lopez D, Scherer C, Stenbach G, Rumilly P, et al. PERIPHERAL NEUROPATHY FOLLOWING FETAL BOVINE CELL RABIES VACCINE. The Lancet. 1986 May;327(8492):1273.

67. Siddiqui A, Usmani RI, Anwer S, Afsar S. Guillain-Barre syndrome occurring after rabies vaccination. JPMA. The Journal of the Pakistan Medical Association. 2005 Feb;55(2):87–8.

68. Knittel T, Ramadori G, Mayet W-J, Löhr H, Meyer Zum Büschenfelde K-H. GUILLAIN-BARRÉSYNDROME AND HUMAN DIPLOID CELL RABIES VACCINE. The Lancet. 1989 Jun;333(8650):1334–5.

69. Israeli E, Agmon-Levin N, Blank M, Shoenfeld Y. Adjuvants and autoimmunity. Lupus. 2009 Nov;18(13):1217–25.

70. WHO | Questions and Answers about macrophagic myofasciitis (MMF). World Health Organization; [cited 2013 May 21]; Available from: http://www.who.int/vaccine_safety/committee/topics/aluminium/questions/en/

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

72. Galli L, Chiappini E, De Martino M. Infections and autoimmunity. The Pediatric infectious disease journal. 2012 Dec;31(12):1295–7.

73. Poland GA, Jacobsen SJ. Influenza vaccine, Guillain-Barré syndrome, and chasing zero. Vaccine. 2012 Aug 31;30(40):5801–3.

74. McCarthy N, Giesecke J. Incidence of Guillain-Barré syndrome following infection with Campylobacter jejuni. American journal of epidemiology. 2001 Mar 15;153(6):610–4.

75. Tam CC, Rodrigues LC, Petersen I, Islam A, Hayward A, O'Brien SJ. Incidence of Guillain-Barré syndrome among patients with Campylobacter infection: a general practice research database study. The Journal of infectious diseases. 2006 Jul 1;194(1):95–7.

76. Carapetis JR, Currie BJ, Good MF. Towards understanding the pathogenesis of rheumatic fever. Scandinavian journal of rheumatology. 1996 Jan;25(3):127–31; discussion 132–3.

77. Eison TM, Ault BH, Jones DP, Chesney RW, Wyatt RJ. Post-streptococcal acute glomerulonephritis in children: clinical features and pathogenesis. Pediatric nephrology (Berlin, Germany). 2011 Mar;26(2):165–80.

78. Kindermann I, Barth C, Mahfoud F, Ukena C, Lenski M, Yilmaz A, et al. Update on Myocarditis. Journal of the American College of Cardiology. 2012 Feb;59(9):779–92.

79. Mayer JL, Beardsley DS. Varicella-associated thrombocytopenia: autoantibodies against platelet surface glycoprotein V. Pediatric research. 1996 Oct;40(4):615–9.

80. Wraith DC, Goldman M, Lambert P-H. Vaccination and autoimmune disease: what is the evidence? Lancet. 2003 Nov 15;362(9396):1659–66.

81. Salemi S, D'Amelio R. Are anti-infectious vaccinations safe and effective in patients with autoimmunity? International reviews of immunology. Informa UK Ltd London, UK; 2010 Jun 3;29(3):270–314.

82. Van Assen S, Elkayam O, Agmon-Levin N, Cervera R, Doran MF, Dougados M, et al. Vaccination in adult patients with auto-immune inflammatory rheumatic diseases: a systematic literature review for the European League Against Rheumatism evidence-based recommendations for vaccination in adult patients with auto-immune inflammatory rheuma. Autoimmun Rev. 2010/12/25 ed. 2011;10(6):341–52.

83. Rahier J-F, Moutschen M, Van Gompel A, Van Ranst M, Louis E, Segaert S, et al. Vaccinations in patients with immune-mediated inflammatory diseases. Rheumatology (Oxford, England). 2010 Oct;49(10):1815–27.

84. Chalmers A, Scheifele D, Patterson C, Williams D, Weber J, Shuckett R, et al. Immunization of patients with rheumatoid arthritis against influenza: a study of vaccine safety and immunogenicity. J Rheumatol. 1994/07/01 ed. 1994;21(7):1203–6.

85. Del Porto F, Lagana B, Biselli R, Donatelli I, Campitelli L, Nisini R, et al. Influenza vaccine administration in patients with systemic lupus erythematosus and rheumatoid arthritis. Safety and immunogenicity. Vaccine. 2006/02/10 ed. 2006;24(16):3217–23.

86. Denman EJ, Denman AM, Greenwood BM, Gall D, Heath RB. Failure of cytotoxic drugs to suppress immune responses of patients with rheumatoid arthritis. Ann Rheum Dis. 1970/05/01 ed. 1970;29(3):220–31.

87. Fomin I, Caspi D, Levy V, Varsano N, Shalev Y, Paran D, et al. Vaccination against influenza in rheumatoid arthritis: the effect of disease modifying drugs, including TNF alpha blockers. Ann Rheum Dis. 2005/07/15 ed. 2006;65(2):191–4.

88. Elkayam O, Bashkin A, Mandelboim M, Litinsky I, Comaheshter D, Levartovsky D, et al. The effect of infliximab and timing of vaccination on the humoral response to influenza vaccination in patients with rheumatoid arthritis and ankylosing spondylitis. Semin Arthritis Rheum. 2009/02/28 ed. 2010;39(6):442–7.

89. Gelinck LB, Van der Bijl AE, Beyer WE, Visser LG, Huizinga TW, Van Hogezand RA, et al. The effect of anti-tumour necrosis factor alpha treatment on the antibody response to influenza vaccination. Ann Rheum Dis. 2007/10/30 ed. 2008;67(5):713–6.

90. Oren S, Mandelboim M, Braun-Moscovici Y, Paran D, Ablin J, Litinsky I, et al. Vaccination against influenza in patients with rheumatoid arthritis: the effect of rituximab on the humoral response. Ann Rheum Dis. 2007/11/06 ed. 2008;67(7):937–41.

91. Kaine JL, Kivitz AJ, Birbara C, Luo AY. Immune responses following administration of influenza and pneumococcal vaccines to patients with rheumatoid arthritis receiving adalimumab. J Rheumatol. 2007/02/17 ed. 2007;34(2):272–9.

92. Mori S, Ueki Y, Hirakata N, Oribe M, Hidaka T, Oishi K. Impact of tocilizumab therapy on antibody response to influenza vaccine in patients with rheumatoid arthritis. Ann Rheum Dis. 2012/08/14 ed. 2012;

93. Kobie JJ, Zheng B, Bryk P, Barnes M, Ritchlin CT, Tabechian DA, et al. Decreased influenza-specific B cell responses in rheumatoid arthritis patients treated with anti-tumor necrosis factor. Arthritis Res Ther. 2011/12/20 ed. 2011;13(6):R209.

94. Kubota T, Nii T, Nanki T, Kohsaka H, Harigai M, Komano Y, et al. Anti-tumor necrosis factor therapy does not diminish the immune response to influenza vaccine in Japanese patients with rheumatoid arthritis. 2007/12/18 ed. 2007;17(6):531–3.

95. Nii T, Kubota T, Nanki T, Komano Y, Harigai M, Kohsaka H, et al. Reevaluation of antibody titers 1 year after influenza vaccination in patients with rheumatoid arthritis receiving TNF blockers. 2008/11/19 ed. 2009;19(2):216–8.

96. Kapetanovic MC, Saxne T, Nilsson JA, Geborek P. Influenza vaccination as model for testing immune modulation induced by anti-TNF and methotrexate therapy in rheumatoid arthritis patients. Rheumatology (Oxford). 2006/11/23 ed. 2007;46(4):608–11.

97. Kivitz, Joy Schechtman, Michele Texter A, Chartash. F and E. Assessment of Immune Responses to Pneumococcal and Influenza Vaccines in Patients with Rheumatoid Arthritis Receiving CertolizumabPegol. ArthritisRheum 63(10-2.Suppl.) pS488 ACRMeetings Chicago,USA abstract. 2011.

98. Gelinck LB, Teng YK, Rimmelzwaan GF, Van den Bemt BJ, Kroon FP, Van Laar JM. Poor serological responses upon influenza vaccination in patients with rheumatoid arthritis treated with rituximab. Ann Rheum Dis. 2007/09/21 ed. 2007;66(10):1402–3.

99. Van Assen S, Holvast A, Benne CA, Posthumus MD, Van Leeuwen MA, Voskuyl AE, et al. Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. Arthritis Rheum. 2009/12/30 ed. 2010;62(1):75–81.

100. Adler S, Krivine A, Weix J, Rozenberg F, Launay O, Huesler J, et al. Protective effect of A/H1N1 vaccination in immune-mediated disease--a prospectively controlled vaccination study. Rheumatology (Oxford). 2011/12/16 ed. 2012;51(4):695–700.

101. Gabay C, Bel M, Combescure C, Ribi C, Meier S, Posfay-Barbe K, et al. Impact of synthetic and biologic disease-modifying antirheumatic drugs on antibody responses to the AS03-adjuvanted pandemic influenza vaccine: a prospective, open-label, parallel-cohort, single-center study. Arthritis Rheum. 2011/03/09 ed. 2011;63(6):1486–96.

102. Iwamoto M, Homma S, Onishi S, Kamata Y, Nagatani K, Yamagata Z, et al. Low level of seroconversion after a novel influenza A/H1N1/2009 vaccination in Japanese patients with rheumatoid arthritis in the 2009 season. Rheumatol Int. 2011/09/02 ed. 2011;

103. Saad CG, Borba EF, Aikawa NE, Silva CA, Pereira RM, Calich AL, et al. Immunogenicity and safety of the 2009 non-adjuvanted influenza A/H1N1 vaccine in a large cohort of autoimmune rheumatic diseases. Ann Rheum Dis. 2011/05/05 ed. 2011;70(6):1068–73.

104. Ribeiro AC, Guedes LK, Moraes JC, Saad CG, Aikawa NE, Calich AL, et al. Reduced seroprotection after pandemic H1N1 influenza adjuvant-free vaccination in patients with rheumatoid arthritis: implications for clinical practice. Ann Rheum Dis. 2011/08/24 ed. 2011;70(12):2144–7.

105. França ILA, Ribeiro ACM, Aikawa NE, Saad CGS, Moraes JCB, Goldstein-Schainberg C, et al. TNF blockers show distinct patterns of immune response to the pandemic influenza A H1N1 vaccine in inflammatory arthritis patients. Rheumatology (Oxford, England). 2012 Nov;51(11):2091–8.

106. Ribeiro AC, Laurindo IM, Guedes LK, Saad CG, Moraes JC, Silva CA, et al. Abatacept severely reduces the immune response to pandemic 2009 influenza A/H1N1 vaccination in patients with rheumatoid arthritis. Arthritis care & research. 2012 Sep 4;

107. Bingham 3rd CO, Looney RJ, Deodhar A, Halsey N, Greenwald M, Codding C, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. Arthritis Rheum. 2009/12/30 ed. 2010;62(1):64–74.

108. Elkayam O, Ablin J, Caspi D. Safety and efficacy of vaccination against streptococcus pneumonia in patients with rheumatic diseases. Autoimmun Rev. 2007/04/07 ed. 2007;6(5):312–4.

109. Elkayam O, Paran D, Caspi D, Litinsky I, Yaron M, Charboneau D, et al. Immunogenicity and safety of pneumococcal vaccination in patients with rheumatoid arthritis or systemic lupus erythematosus. Clin Infect Dis. 2001/12/12 ed. 2002;34(2):147–53.

110. Kapetanovic MC, Saxne T, Sjoholm A, Truedsson L, Jonsson G, Geborek P. Influence of methotrexate, TNF blockers and prednisolone on antibody responses to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis. Rheumatology (Oxford). 2005/11/17 ed. 2006;45(1):106–11.

111. Visvanathan S, Keenan GF, Baker DG, Levinson AI, Wagner CL. Response to pneumococcal vaccine in patients with early rheumatoid arthritis receiving infliximab plus methotrexate or methotrexate alone. J Rheumatol. 2007/04/21 ed. 2007;34(5):952–7.

112. Kapetanovic MC, Roseman C, Jonsson G, Truedsson L, Saxne T, Geborek P. Antibody response is reduced following vaccination with 7-valent conjugate pneumococcal vaccine in adult methotrexate-treated patients with established arthritis, but not those treated with tumor necrosis factor inhibitors. Arthritis Rheum. 2011/08/13 ed. 2011;63(12):3723–32.

113. Kapetanovic MC, Roseman C, Jonsson G, Truedsson L. Heptavalent pneumococcal conjugate vaccine elicits similar antibody response as standard 23-valent polysaccharide vaccine in adult patients with RA treated with immunomodulating drugs. Clin Rheumatol. 2011/10/01 ed. 2011;30(12):1555–61.

114. Elkayam O, Caspi D, Reitblatt T, Charboneau D, Rubins JB. The effect of tumor necrosis factor blockade on the response to pneumococcal vaccination in patients with rheumatoid arthritis and ankylosing spondylitis. Semin Arthritis Rheum. 2004/02/24 ed. 2004;33(4):283–8.

115. Gelinck LB, Van der Bijl AE, Visser LG, Huizinga TW, Van Hogezand RA, Rijkers GT, et al. Synergistic immunosuppressive effect of anti-TNF combined with methotrexate on antibody responses to the 23 valent pneumococcal polysaccharide vaccine. Vaccine. 2008/05/27 ed. 2008;26(27-28):3528–33.

116. Tay L, Leon F, Vratsanos G, Raymond R, Corbo M. Vaccination response to tetanus toxoid and 23-valent pneumococcal vaccines following administration of a single dose of abatacept: a randomized, open-label, parallel group study in healthy subjects. Arthritis research & therapy. 2007 Jan;9(2):R38.

117. Schiff M, Kaell A, Vratsanos G BK. Response to pneumococcal vaccine in rheumatoid arthritis patients with an inadequate response to anti-TNF therapy treated with abatacept in the ARRIVE trial. Ann Rheum Dis. 2007;66 (S11):437.

118. Mori S, Ueki Y, Akeda Y, Hirakata N, Oribe M, Shiohira Y, et al. Pneumococcal polysaccharide vaccination in rheumatoid arthritis patients receiving tocilizumab therapy. Annals of the rheumatic diseases. 2013 Jan 23;

119. Devey ME, Bleasdale K, Isenberg DA. Antibody affinity and IgG subclass of responses to tetanus toxoid in patients with rheumatoid arthritis and systemic lupus erythematosus. Clin Exp Immunol. 1987/06/01 ed. 1987;68(3):562–9.

120. Elkayam O, Yaron M, Caspi D. Safety and efficacy of vaccination against hepatitis B in patients with rheumatoid arthritis. Ann Rheum Dis. 2002/06/25 ed. 2002;61(7):623–5.

121. Erguven M, Kaya B, Hamzah OY, Tufan F. Evaluation of immune response to hepatitis A vaccination and vaccine safety in juvenile idiopathic arthritis. Journal of the Chinese Medical Association : JCMA. 2011 May;74(5):205–8.

122. ter Waarbeek H, Dukers-Muijrers N, Hoebe C, editors. A Study of the Effectiveness of Hepatitis A Vaccination in Travelers with Immunosuppressive Medication. 11th Conference of the International Society of Travel Medicine; 2009; Budapest, Hungary.

123. Heijstek MW, Pileggi GCS, Zonneveld-Huijssoon E, Armbrust W, Hoppenreijs EPAH, Uiterwaal CSPM, et al. Safety of measles, mumps and rubella vaccination in juvenile idiopathic arthritis. Annals of the rheumatic diseases. 2007 Oct;66(10):1384–7.

124. Borte S, Liebert UG, Borte M, Sack U. Efficacy of measles, mumps and rubella revaccination in children with juvenile idiopathic arthritis treated with methotrexate and etanercept. Rheumatology (Oxford, England). 2009 Feb;48(2):144–8.

125. Heijstek MW, Gorter S, Vries LD De, Smits GP, Gageldonk PG Van, Berbers GAM, et al. Effects of the Live Attenuated Measles-Mumps-Rubella Booster Vaccination With Juvenile Idiopathic Arthritis. JAMA. 2013 Jun 19;309(23):2449-56.

126. Pileggi GS, De Souza CBS, Ferriani VPL. Safety and immunogenicity of varicella vaccine in patients with juvenile rheumatic diseases receiving methotrexate and corticosteroids. Arthritis care & research. 2010 Jul;62(7):1034–9.

127. Zhang J, Xie F, Delzell E, Chen L, Winthrop KL, Lewis JD, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. JAMA : the journal of the American Medical Association. 2012 Jul 4;308(1):43–9.

128. Prevention of Herpes Zoster Recommendations of the Advisory Committee on Immunization Practices (ACIP) [Internet]. [cited 2012 Nov 12]. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5705a1.htm

129. Mota LM, Oliveira AC, Lima RA, Santos-Neto LL, Tauil PL. [Vaccination against yellow fever among patients on immunosuppressors with diagnoses of rheumatic diseases]. Rev Soc Bras Med Trop. 2009/03/17 ed. 2009;42(1):23–7.

130. Scheinberg M, Guedes-Barbosa LS, Mangueira C, Rosseto EA, Mota L, Oliveira AC, et al. Yellow fever revaccination during infliximab therapy. Arthritis Care Res (Hoboken). 2010/06/11 ed. 2010;62(6):896–8.

131. Kernéis S, Launay O, Ancelle T, Iordache L, Naneix-Laroche V, Méchaï F, et al. Safety and immunogenicity of yellow fever 17D vaccine in adults receiving systemic corticosteroid therapy: An observational cohort study. Arthritis care & research. 2013 Apr 1;

132. Williams GW, Steinberg AD, Reinertsen JL, Klassen LW, Decker JL, Dolin R. Influenza immunization in systemic lupus eruthematosus. A double-blind trial. 1978/06/01 ed. 1978;88(6):729–34.

133. Brodman R, Gilfillan R, Glass D, Schur PH. Influenzal vaccine response in systemic lupus erythematosus. 1978/06/01 ed. 1978;88(6):735–40.

134. Ristow SC, Douglas RG, Condemi JJ. Influenza vaccination of patients with systemic lupus erythematosus. Annals of internal medicine. 1978 Jun;88(6):786–9.

135. Mercado U, Acosta H, Avendano L. Influenza vaccination of patients with systemic lupus erythematosus. 2004/05/18 ed. 2004;56(1):16–20.

136. Holvast A, Huckriede A, Wilschut J, Horst G, De Vries JJ, Benne CA, et al. Safety and efficacy of influenza vaccination in systemic lupus erythematosus patients with quiescent disease. Ann Rheum Dis. 2005/12/03 ed. 2006;65(7):913–8.

137. Wiesik-Szewczyk E, Romanowska M, Mielnik P, Chwalinska-Sadowska H, Brydak LB, Olesinska M, et al. Anti-influenza vaccination in systemic lupus erythematosus patients: an analysis of specific humoral response and vaccination safety. Clin Rheumatol. 2010/02/09 ed. 2010;29(6):605–13.

138. Kostianovsky A, Charles P, Alves JF, Goulet M, Pagnoux C, Le Guern V, et al. Immunogenicity and safety of seasonal and 2009 pandemic A/H1N1 influenza vaccines for patients with autoimmune diseases: a prospective, monocentre trial on 199 patients. Clin Exp Rheumatol. 2012/07/26 ed. 2012;30(1 Suppl 70):S83–9.

139. Setti M, Fenoglio D, Ansaldi F, Filaci G, Bacilieri S, Sticchi L, et al. Flu vaccination with a virosomal vaccine does not affect clinical course and immunological parameters in scleroderma patients. Vaccine. 2009/02/10 ed. 2009;27(25-26):3367–72.

140. Crowe SR, Merrill JT, Vista ES, Dedeke AB, Thompson DM, Stewart S, et al. Influenza vaccination responses in human systemic lupus erythematosus: impact of clinical and demographic features. Arthritis and rheumatism. 2011 Aug;63(8):2396–406.

141. Urowitz MB, Anton A, Ibanez D, Gladman DD. Autoantibody response to adjuvant and nonadjuvant H1N1 vaccination in systemic lupus erythematosus. Arthritis care & research. 2011 Nov;63(11):1517–20.

142. Borba EF, Saad CGS, Pasoto SG, Calich ALG, Aikawa NE, Ribeiro ACM, et al. Influenza A/H1N1 vaccination of patients with SLE: can antimalarial drugs restore diminished response under immunosuppressive therapy? Rheumatology (Oxford, England). 2012 Jun;51(6):1061–9.

143. Mathian A, Devilliers H, Krivine A, Costedoat-Chalumeau N, Haroche J, Huong DB-LT, et al. Factors influencing the efficacy of two injections of a pandemic 2009 influenza A (H1N1) nonadjuvanted vaccine in systemic lupus erythematosus. Arthritis and rheumatism. 2011 Nov;63(11):3502–11.

144. Tarjan P, Sipka S, Marodi L, Nemes E, Lakos G, Gyimesi E, et al. No short-term immunological effects of Pneumococcus vaccination in patients with systemic lupus erythematosus. Scand J Rheumatol. 2002/10/09 ed. 2002;31(4):211–5.

145. Battafarano DF, Battafarano NJ, Larsen L, Dyer PD, Older SA, Muehlbauer S, et al. Antigen-specific antibody responses in lupus patients following immunization. Arthritis Rheum. 1998/10/20 ed. 1998;41(10):1828–34.

146. Jarrett MP, Schiffman G, Barland P, Grayzel AI. Impaired response to pneumococcal vaccine in systemic lupus erythematosus. Arthritis Rheum. 1980/11/01 ed. 1980;23(11):1287–93.

147. Elkayam O, Paran D, Burke M, Zakut V, Ben-Yitshak R, Litinsky I, et al. Pneumococcal vaccination of patients with systemic lupus erythematosus: effects on generation of autoantibodies. Autoimmunity. 2005 Nov;38(7):493–6.

148. Mercado U, Acosta H, Diaz-Molina R. Antibody response to pneumococcal polysaccharide vaccine in systemic sclerosis. J Rheumatol. 2009/07/02 ed. 2009;36(7):1549–50.

149. Lipnick RN, Karsh J, Stahl NI, Blackwelder WC, Schiffman G, Klippel JH. Pneumococcal immunization in patients with systemic lupus erythematosus treated with immunosuppressives. J Rheumatol. 1985/12/01 ed. 1985;12(6):1118–21.

150. McDonald E, Jarrett MP, Schiffman G, Grayzel AI. Persistence of pneumococcal antibodies after immunization in patients with systemic lupus erythematosus. J Rheumatol. 1984/06/01 ed. 1984;11(3):306–8.

151. Nies K, Boyer R, Stevens R, Louie J. Anti-tetanus toxoid antibody synthesis after booster immunization in systemic lupus erythematosus. Comparison of the in vitro and in vivo responses. Arthritis Rheum. 1980/12/01 ed. 1980;23(12):1343–50.

152. Kuruma KA, Borba EF, Lopes MH, De Carvalho JF, Bonfa E. Safety and efficacy of hepatitis B vaccine in systemic lupus erythematosus. Lupus. 2007/06/20 ed. 2007;16(5):350–4.

153. Mok CC, Ho LY, Fong LS, To CH. Immunogenicity and safety of a quadrivalent human papillomavirus vaccine in patients with systemic lupus erythematosus: a case-control study. Annals of the rheumatic diseases. 2012 May 15;

154. Mease PJ, Ritchlin CT, Martin RW, Gottlieb AB, Baumgartner SW, Burge DJ, et al. Pneumococcal vaccine response in psoriatic arthritis patients during treatment with etanercept. J Rheumatol. 2004/07/02 ed. 2004;31(7):1356–61.

155. Roseman C, Truedsson L, Kapetanovic MC. The effect of smoking and alcohol consumption on markers of systemic inflammation, immunoglobulin levels and immune response following pneumococcal vaccination in patients with arthritis. Arthritis Res Ther. 2012/07/25 ed. 2012;14(4):R170.

156. Salinas GF, De Rycke et al. L. TNF Alpha Impairs Humoral T Cell Dependent Antibody Responses. Philadelphia; 2009.

157. Franco Salinas G, De Rycke L, Barendregt B, Paramarta JE, Hreggvidstdottir H, Cantaert T, et al. Anti-TNF treatment blocks the induction of T cell-dependent humoral responses. Annals of the rheumatic diseases. 2013 Jun;72(6):1037–43.

158. Holvast A, Stegeman CA, Benne CA, Huckriede A, Wilschut JC, Palache AM, et al. Wegener's granulomatosis patients show an adequate antibody response to influenza vaccination. Ann Rheum Dis. 2008/07/16 ed. 2009;68(6):873–8.

159. Zycinska K, Romanowska M, Nowak I, Rybicka K, Wardyn KA, Brydak LB. Antibody response to inactivated subunit influenza vaccine in patients with Wegener's granulomatosis. 2008/03/28 ed. 2007;58 Suppl 5(Pt 2):819–28.

160. Hugle T, Bircher A, Walker UA. Streptococcal hypersensitivity reloaded: severe inflammatory syndrome in Behcet's disease following 23-valent polysaccharide Streptococcus pneumoniae vaccine. Rheumatology (Oxford). 2011/12/14 ed. 2012;51(4):761–2.

161. Erkek E, Ayaslioglu E, Erkek AB, Kurtipek GS, Bagci Y. Response to vaccination against hepatitis B in patients with Behcet's disease. J Gastroenterol Hepatol. 2005/09/22 ed. 2005;20(10):1508–11.

162. Visser LG. The immunosuppressed traveler. Infectious disease clinics of North America. 2012 Sep;26(3):609–24.

163. Schweizerische Gesellschaft für Rheumatologie. Impfempfehlungen für Patienten mit entzündlich-rheumatischen Erkrankungen. 2010.