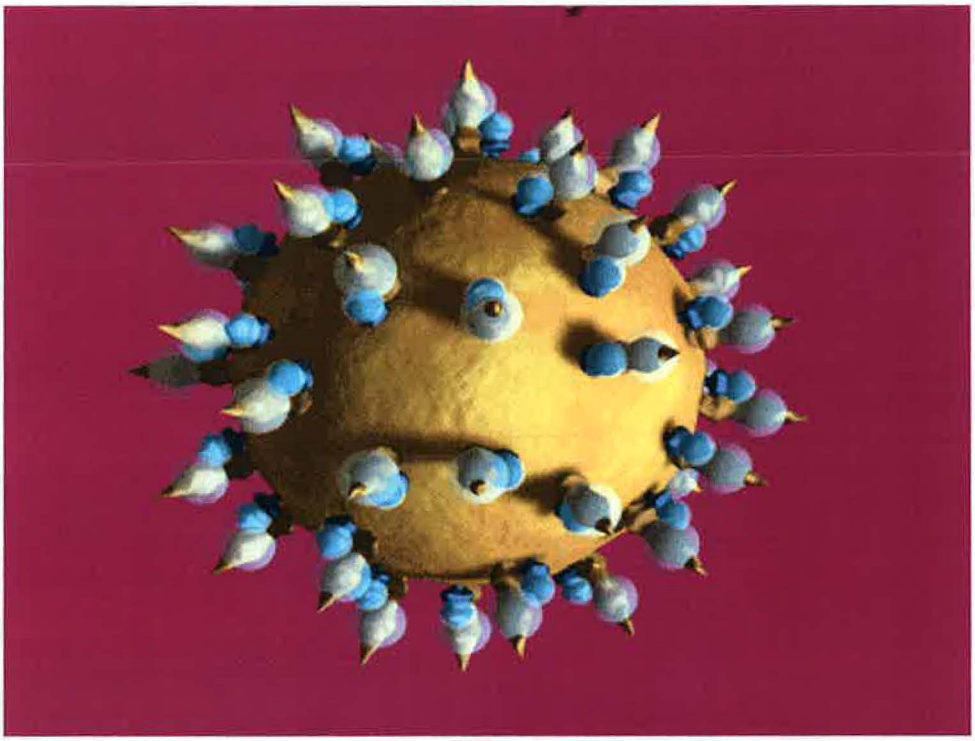
Viruses and Arthritis: New Challenges for Therapy



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Internal Medicine Grand Rounds
May 29, 2009
Dr. Reimold will discuss off-label uses of medications in this presentation.

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Interests:
Epidemiology of rheumatoid arthritis and spondyloarthritides
Biologic therapies
Gene expression in the rheumatic diseases.

Viruses Causing Arthritis

An association of viruses and musculoskeletal symptoms is so common that arthralgias and myalgias can be part of essentially all acute viral infections. Even an actual arthritis, with inflammation of joints manifested as swelling, pain, redness, and heat, may be part of a viral syndrome for a few weeks, with eventual spontaneous resolution in most cases. The ACR criteria for rheumatoid arthritis (RA) include an important provision requiring the presence of true arthritis for at least 6 weeks in order to help exclude a transient viral arthritis that is not destined to be an ongoing illness.

The list of viruses associated with arthritis is shown in Table 1. Musculoskeletal symptoms can occur as part of the viral syndrome, but increasingly, the clinical challenges arise from recognizing concomitant rheumatic diseases and in choosing therapies that minimize increased viral replication and organ damage. In today's presentation, we will therefore consider rheumatic syndromes resulting from chronic viral infection and viral latency. We will highlight the diagnosis and therapy of rheumatoid arthritis in the setting of hepatitis C virus. Finally, we will consider the challenges preventing viral infection by vaccination in a population that may be immunocompromised based on their inflammatory disease as well as its therapy.

Table 1. Viruses Causing Arthritis

- Hepatitis A, B, and C
- HIV
- Parvovirus
- Genus Alphavirus, Family Togaviridae
    - Ross River virus
    - Barmah Forest virus
    - Sindbis viruses (Karelian fever)
    - Mayaro
    - O'nyong'nyong
    - Chikungunya
- Rubella/rubella vaccine
- Mumps
- Enterovirus: Coxsackie, Echovirus
- Herpes:
    - Varicella
    - Epstein-Barr
    - Herpes simplex
    - Cytomegalovirus

The Natural History of Hepatitis C Infection.

Hepatitis C is a linear, single-stranded RNA virus discovered in 1988. There are 6 subtypes of the virus, which has implications for responsiveness to therapy. The prevalence in the US population is at 1 to 2%, or about 3.5 million cases. Among US veterans, the prevalence has been reported as 5.4 to 6.6%. There are an estimated 150,000 new US cases annually (1). Transmission is parenteral in about 50% of cases, with the mode of transmission unclear in the other 50%. Hepatitis C causes up to 10,000 deaths annually. By 2010, deaths from hepatitis C will exceed those from HIV (2).

The incubation period for hepatitis C is 6 weeks. About 25% of cases develop jaundice. After the initial infection, 15% clear the virus spontaneously, and 60 to 85% develop chronic infection. 20 to 50% of chronic hepatitis C patients develop cirrhosis and have an increased risk of hepatocellular carcinoma. Mixed cryoglobulinemia can be found in up to 50% of chronic hepatitis C patients.

The initial diagnosis of hepatitis C is usually made by anti-viral antibodies, either by EIA (sensitivity of 80-90%, but false positives seen with hypergammaglobulinemia, positive rheumatoid factor, or recent influenza immunization) or by RIBA (recombinant immunoblot assay, with sensitivity and specificity each at 95%). A positive antibody can be confirmed by measuring hepatitis C viral RNA by PCR. The presence of hepatitis C is frequently associated with positive tests of autoimmune phenomena. For example, the ANA is positive (usually low to intermediate titer) in 10-30% of HCV patients; the rheumatoid factor is positive in 60 to 80% of HCV patients (again usually low to intermediate titers); and anti-smooth muscle antibody is found in 60 to 70% of HCV patients. In those patients who are candidates for therapy, the treatment of hepatitis C virus relies on pegylated interferon-α with ribavirin. Cytotoxic therapy is used in those patients with severe vasculitis, and corticosteroids may be employed as well in the setting of organ-threatening disease, despite the risk of increased viral replication.

There are numerous potential extrahepatic manifestations of hepatitis C. Thyroiditis and diabetes are described, as are cytopenias and lymphoproliferative disorders. Of particular interest in rheumatology, HCV can exhibit sialotropism and therefore destroy the salivary glands, resulting in Sjogren's syndrome. Furthermore, an atypical antiphospholipid syndrome and sarcoidosis both have an association with HCV infection.

The Role of TNFα in Hepatitis C Infection.

Hepatitis C is associated with the presence of numerous pro-inflammatory as well as anti-inflammatory cytokines, chemokines, and their receptors. For example, chronic hepatitis C shows high serum IL-1, IL-2, IL-4, IL-6, TNFα, IFNα, and IFN-γ Furthermore, sIL-2R, TNFα, IL-10, IL-18 are higher in chronic HCV than in asymptomatic HCV or healthy controls. Persistent responders to IFNα plus ribavirin had higher IFN-γ and lower IL-4, indicating that the Th1 lymphocyte phenotype is somewhat protective while Th2 predominance has more HCV replication and poorer therapeutic response (3). While such

studies generally show more hepatic inflammation in patients with elevated TNFα levels, TNFα does not act in a solitary manner and was associated with the most active cytolysis when present along with IL-1, IL-2, IL-4, and IL-6 (4).

A study of two TNFα promoter polymorphisms and one IL-10 promoter polymorphism was undertaken in.18 patients who cleared their HCV infection, 42 chronic HCV patients, and 135 healthy Sicilians. Those recovering from the HCV infection had less of the high-producing TNFα promoter, and more of the high-producing IL-10 promoter (generating an anti-inflammatory effect) (5). More recently, the observation has been made that TLR2 (Toll-like receptor 2) and TLR4 are elevated in PBMCs of chronic HCV patients, regardless of HCV genotype or histology of disease. Increased monocyte expression of TLR2 correlated with increased circulating TNFα levels, hepatic inflammation, and necrosis. As in several other studies, TNFα levels were significantly increased in HCV patients (6).

The presence of HCV infection is also associated with elevated risk for type 2 diabetes (DM) (7, 8). 20% of cirrhotics develop DM, regardless of etiology, and 13-33% of HCV patients develop diabetes even without cirrhosis. The cytokine TNFα causes insulin resistance and represents a possible connection between HCV infection and DM. Even non-diabetic HCV patients are more likely to have insulin resistance and defects in insulin-signaling pathways. In addition, diabetic HCV patients have higher levels of soluble TNFαR compared to non-diabetic HCV patients and controls (9, 10). The importance of TNFα in these pathways is highlighted by the example of obese mice with knockout of the TNFα gene or their receptors, who remained insulin sensitive despite marked weight gain (11)

Rheumatologic Features of Hepatitis C Infection

Hepatitis C is known to cause two types of arthritic syndromes. The two subsets are: 1. A polyarthritis of small joints similar to RA but milder, rarely associated with erosions, and 2. A mono- or oligoarthritis with an intermittent course, often with cryoglobulins (type II or III, with palpable purpura, glomerulonephritis, and peripheral neuropathy) (12). Traditional therapies for the symptoms include NSAIDs, low-dose steroids, and hydroxychloroquine (13).

About 80% of cases of cryoglobulinemic vasculitis are associated with the presence of hepatitis C (14). It is a small- to medium-vessel immune complex-mediated vasculitis. The HCV is not integrated into host genome and produces a chronic immune stimulus. More specifically, the HCV envelope protein E2 interacts with B cell CD81 receptor, increasing VDJ rearrangement. Such a mechanism of B lymphocyte activation may be a part of increased immunoglobulin production, including that of rheumatoid factor or mixed cryoglobulins. Furthermore, antiapoptotic signals including proto-oncogenes such as Bcl-2 are activated. The resulting extended B cell survival again becomes part of increased antibody production and even B-cell lymphoma. Therapies for cryoglobulinemic vasculitis are antiviral to eliminate the underlying immune stimulus, symptomatic (corticosteroids and plasmapheresis) to achieve short-term reduction in

cryoglobulin levels, and pathogenic (cyclophosphamide as would be used in other forms of vasculitis, and rituximab to target the B lymphocyte pool).

Sjogren's syndrome is associated with hepatitis C infection and has several features that differ from the syndrome in the general population. In the presence of hepatitis C, Sjogren's syndrome affects more males, is only occasionally ANA+ and anti-SSA/SSB+, shows milder minor salivary gland biopsy findings with less lymphocytic infiltration, and clinically results in less xerophthalmia.

Diagnosis of Rheumatoid Arthritis in the Presence of Hepatitis C.

Referral of a patient with arthritic symptoms and a positive rheumatoid factor is a common consult in rheumatology. However, we have seen that a low to moderate elevation of RF is very common in the presence of hepatitis C, reflecting the chronic antigenic stimulation from the virus. It has become a standard part of a workup for inflammatory arthritis to determine hepatitis C (and B) status, to help in diagnosis of the arthritis and to allow an informed decision about future use of hepatotoxic medications.

The anti cyclic citrullinated antibody has become a valuable tool to augment rheumatoid factor determination in patients undergoing evaluation for the presence of rheumatoid arthritis. Citrullinated proteins result from the enzymatic action of peptidyl arginine deiminase to convert arginine into citrulline (Figure 1). These proteins are immunogenic and elicit an antibody response, and are found in high concentrations in the joints. A metaanalysis of 87 studies has derived a sensitivity of 67% and specificity of 95% for aCCP in the diagnosis of RA (compared to 69% and 85%, respectively, for the IgM rheumatoid factor) (15). Anti-CCP can be found in other conditions, including tuberculosis, where there is some evidence that it binds to epitopes that do not contain a citrullinated peptide, and at generally low titer in multiple rheumatic diseases (polymyositis/dermatomyositis 23% positive, SLE 15%, Sjogren's 14%, scleroderma 6%)(16). Studies are accumulating that link the presence of anti-CCP to more severe joint damage from RA and more rapid progression in early RA (17, 18).

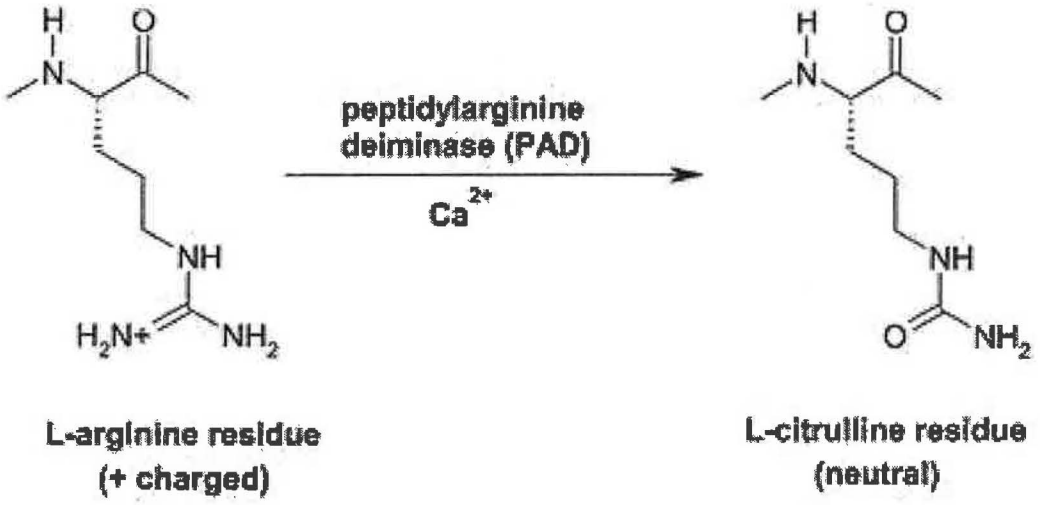

Figure 1. Generation of citrulline residues by the deimination of arginine.

Unlike rheumatoid factor, the anti-CCP antibodies are generally not associated with hepatitis C infection. In small studies of hepatitis C patient undergoing evaluation for RA, Abdel Baky et al (19) presented that 7 of 8 patients with typical clinical RA and +RF were positive for aCCP, while of 10 patients with normal joints, only 1 (10%) had a positive aCCP (Figure 2). None of 16 healthy controls had a positive aCCP. Several similar relatively small studies have confirmed that aCCP is present in up to 80% of patients with HCV and clinical inflammatory arthritis, but in less than 10% of patients with HCV and no arthritis. Further follow-up is needed to know if some of the latter aCCP positive patients are destined to develop rheumatoid arthritis in the future.

66 patients	**aCCP Positive (%)**
21 with RA, +RF, negative HCV	16/21 (76%)
8 with chronic HCV and RA, +RF	7/8 (88%)
11 with HCV, undifferentiated polyarthralgia/arthritis, RF+	3/11 (27%)
10 with HCV, normal joints	1/10 (10%)
16 healthy controls	0 (0%)

Figure 2. Use of anti-CCP antibody to aid in the diagnosis of rheumatoid arthritis in patients with hepatitis C.

Biologic medication in the treatment of rheumatic diseases.

There are now eight biologic medications with indications in rheumatic diseases (Table 2). Five of these are TNFα antagonists (etanercept, infliximab, adalimumab, and the recently FDA-approved certolizumab and golimumab). Besides their use in rheumatoid arthritis, some of these agents have FDA-approved uses in psoriatic arthritis and skin psoriasis, ankylosing spondylitis, and inflammatory bowel disease (20).

	Trade Name	Description	Route
Anti- TNFα			
Etanercept	Enbrel	Receptor Fusion Protein	SubQ
Infliximab	Remicade	mAb	IV
Adalimumab	Humira	mAb	SubQ
Certolizumab	Cimzia	mAb	SubQ
Golimumab	Simponi	mAb	SubQ
IL-1 RA			
Anakinra	Kineret	Receptor antagonist	SubQ
T Cell Costimulation Blockade			
Abatacept	Orencia	CTLA4-Ig Fusion Protein	IV
Anti CD20 (B Cell)			
Rituximab	Rituxan	mAb	IV

Table 2. Biologic medications with FDA-approved indications in selected rheumatic diseases.

TNFα Antagonists in the Treatment of Hepatitis C

Since the elevation of the cytokine TNFα is part of the inflammatory response to hepatitis C in the liver, initial studies have been done to evaluate whether blockade of TNFα would be a helpful therapeutic adjunct in the eradication of hepatitis C infection. The only published randomized study testing this hypothesis consisted of 50 hepatitis C patients, randomized into two groups of 25 each (21). Both groups were treated with interferon-α and ribavirin, while one group additionally received etanercept injections for 24 weeks, while the other received placebo injections. Six patients in the etanercept group were excluded before the first treatment (4 personal reasons, 1 no insurance, 1 normal ALT). By week 24, the etanercept group of 19 patients had 2 discontinuations for adverse events and 5 for persistence of HCV RNA, leaving 12 patients who were followed to liver biopsy at week 52. The placebo group of 25 patients by week 24 had 1

withdrawal due to adverse events, and 16 dicontinuations for persistence of HCV RNA. Therefore, 12 of 19 (63%) etanercept patients and 8 of 25 (32%) placebo patients had negative HCV RNA titers and qualified for completion of the study. This difference was statistically significant (p=0.04). Even nonresponders had a decline in HCV RNA levels in the etanercept group.

A study using a single dose of infliximab at the start of hepatitis C therapy was presented as an abstract in 2007 (22). The population was carefully selected to include only treatment-naïve patients with HCV genotype 1 and high TNFα levels (> 300 pg/mL). The study was a randomized, prospective, open-label trial of peginterferon α-2b plus ribavirin, with or without a single dose of infliximab. Study endpoints were an early virologic response and a sustained virologic response. The results showed that patients receiving a dose of infliximab had a more rapid virologic response (in 43.8% vs. 30.8%), had significantly more patients with undetectable HCV RNA at week 8 (in 69% vs. 46%, p=0.024), but had equivalent percentages with undetectable HCV RNA by week 12 (69% vs. 85%, p=0.183). Therefore, the group receiving conventional therapy eventually had an equivalent virologic outcome to the infliximab group despite their rapid early response. It remains to be studied whether a different TNFα antagonist dosing regimen or a particular subset of HCV patients will benefit substantially from this treatment approach. The two available studies do suggest that the addition of anti-TNFα therapy is associated with more rapid clearance of HCV in responders.

Use of TNFα Antagonists in Arthritis Patients with Hepatitis C.

Apart from use of a TNFα antagonist in the treatment of the viral infection, clinicians have repeatedly seen patients with hepatitis C whose rheumatoid arthritis was not adequately controlled on traditional DMARD therapy. Experience has steadily grown as case reports and case series have accumulated, along with 1 controlled trial. Even in the absence of hepatitis C, the use of TNFα antagonists is already known to result in ANA induction (in about 30% of cases) and even anti-dsDNA induction (in up to 15%), with only rare clinical episodes of SLE. With this background, Vauloup et al investigated immunologic changes occurring in RA patients with hepatitis C who were beginning TNFα antagonists (23). Of their 6 patients, 2 had induction of ANA, 3 induction of anti-dsDNA antibodies. None had new onset of ENA (extractable nuclear antigen), SMA (smooth muscle) or LKM-1 (anti-liver/kidney/microsome). Cryoglobulinemia appeared in 2 patients and persisted in 2 others.

Treatment using TNFα antagonists for rheumatic disease in the presence of hepatitis C has been reported in at least 100 cases (24, 25). Despite some variation, liver function tests have not increased, exacerbation of hepatitis has not been reported, and viral loads have generally remained stable. There have been no cases of fulminant hepatitis C. Two case reports have been presented where patients had an increase in hepatitis C viral loads while receiving etanercept for rheumatoid arthritis, but for both the baseline viral load was not determined at the time of etanercept initiation, making the interpretation of hepatitis C reactivation problematic (25). The overall conclusion is that use of

etanercept, infliximab, and adalimumab in patients with hepatitis C has been quite safe, with no catastrophic complications reported.

The ACR 2008 guidelines on use of biologic agents in the setting of viral hepatitis considered acute hepatitis B and C a contraindication. For chronic hepatitis B and C, whether treated or untreated, the expert panel considered the severity of liver dysfunction (by Child-Pugh scoring system) to play an important role. The Child-Pugh system factors in five indicators of liver function: serum albumin, total bilirubin, prothrombin time, presence of ascites, and presence of encephalopathy. The biologic agents were considered contraindicated for treated as well as untreated hepatitis B and C, if patients had Child-Pugh class B (significant functional compromise) or class C (decompensated). The published case reports of TNFα antagonist use in the setting of hepatitis C rarely mention Child-Pugh classification, but based on available information, are predominantly class A (well-compensated disease).

Even though hepatitis B and C are discussed together in the ACR recommendations, the published experience with hepatitis B and TNFα antagonists is not as benign as that for hepatitis C. For hepatitis B, 2 of 3 HBV+ patients with Crohn's disease in a series of 80 infliximab recipients had reactivation of hepatitis B, with 1 death (26). The one HBV+ patient on lamivudine in this series did not have reactivation, although development of resistance to this antiviral is described after 6 to 9 months of use. A separate series of patients described 70 HBcAb (IgG)-positive, HBsAg-negative cases in a series of 225 patients (27). Twenty percent of these subjects had a persistent elevation in AST and ALT, not ascribable to other medications. Unfortunately, viral titers or other confirmation of hepatitis B activation were not presented. The conclusion from these studies is that the presence of hepatitis B virus may not be fully evaluated until hepatitis B core studies are done, and that hepatitis B reactivation can occur in association with TNFα antagonist administration. Where the clinical decision is made to accept these risks, use of an antiviral such as lamivudine or adefovir dipivoxil (Hepsera, Preveon) is important to lower the risk of viral reactivation.

In summary, the use of TNFα antagonists to treat rheumatic conditions in patients with hepatitis C and well-compensated liver function appears safe from published reports of the initial approximately 100 patients. Rheumatologists have but rarely ordered baseline liver biopsies, although this could give additional information. Monitoring of liver functions (AST, ALT) is recommended, and published cases often have data on HCV viral load over time. There should be extra caution in heavily immunosuppressed patients, such as transplant recipients, who may have an increased rate of hepatitis C progression.

Preventing Viral Infections: Immunization

The theoretical concern of whether TNFα antagonists could decrease responses to immunization arises out of in vitro studies. It has been observed that TNFα blockade suppresses the differentiation of osteoclasts, which may be beneficial in terms of reducing bone erosions. However, recent evidence also showed that osteoclasts also

support the survival of plasma cells in vitro, assuring the stable presence of the cell type that produces the bulk of all antibodies (28). In addition, it was also recently demonstrated that TNFα blockade in RA results in decreased germinal center B cells and peripheral memory B cells. Again, both cell types are integral to the pathway of antibody production (29).

Influenza

A major obstacle to achieving immunity to influenza virus is the lack of immunization of patients at risk. Lanternier studied this problem in 138 French patients in 2005-2006 who had an inflammatory disease or were taking immunosuppressive medication (30). 39% of the patients had a reason for receiving an annual flu shot (e.g. age $\geq$ 65), and of these 47.2% were actually vaccinated. By contrast, 61% of the study group had the inflammatory disease or immunosuppression as their only reason for needing a flu shot, and only 16.7% of the group were vaccinated. During the same year, the immunization rate for the French general population aged $\geq$65 was 70.1%. The main reasons for lack of vaccination were failure of the physician to suggest it (58%) and fear of side effects (35%).

By comparison, the current CDC recommendations for influenza vaccination include these guidelines (31):

1. Ages 6 months to 18 years, AND age $\geq$ 50 years.
2. Women who will be pregnant in flu season
3. Long-term health problems:
    a. Heart disease
    b. Lung disease and asthma
    c. Kidney disease
    d. Liver disease
    e. Metabolic disease, such as diabetes
    f. Anemia, and other blood disorders
4. Weakened immune system
    a. HIV/AIDS or other diseases affecting the immune system
    b. Long-term treatment with drugs such as steroids
    c. Cancer treatment (Radiotherapy, drugs)
5. Certain muscle or nerve disorders (seizures, cerebral palsy) that can lead to breathing or swallowing problems.
6. Long-term aspirin treatment in those ages 6 mos to 18 years (risk of Reye Syndrome)
7. Residents of nursing home and other chronic-care facilities.
8. Those who live with or care for people at high risk of influenza-related populations
    a. Health care providers
    b. Household contacts and caregivers of children up to age 5 years
    c. Household contacts and caregivers of people $\geq$50 years old or of those with elevated risk of severe influenza-related complications
9. Those providing essential community services
10. Those living in dormitories, correctional facilities, or crowded conditions.

11. Travelers/tourists.
12. Anyone who wants to reduce their risk of becoming ill with influenza or of spreading influenza.

While rheumatic diseases are not singled out on these recommendations, such patients would generally be recommended for immunization based on having "other disease affecting the immune system" (item 4a), taking medications affecting the immune system (item 4b), age range (item 1), or for reducing the risk of becoming ill with influenza (item 12). Even when the patient is properly immunized, the recommendations also suggest immunization of household contacts and caregivers, a point that may not be sufficiently emphasized by medical providers.

Influenza immunization success has been studied in several rheumatic diseases and in the presence of immunosuppressive or biologic medication. A four-fold rise in the antibody titer to the specific influenza strains in the vaccine is used in several studies as a surrogate marker for an adequate response. It has been found that the standard DMARD used in RA, methotrexate, does not impair antibody responses to influenza vaccine. However, use of methotrexate with etanercept or with infliximab leads to reduced titers of antibody and lower response rates (32). In these studies, protective titers at baseline also predict worse antibody responses. On the other hand, adalimumab, used with or without methotrexate, showed no reduction in response to influenza vaccine (33). Therefore, this represents one finding that differentiates among the TNFα inhibitors, which are felt to be therapeutically equivalent for RA (Table 3).

Antibodies to influenza also persist normally in RA patients, as studied in a Japanese report. After 1 year, as patients presented for the next year's immunization, antibody levels were equivalent in healthy controls, RA patients on oral DMARDs, and RA patients on etanercept or infliximab (34). Control titers of mumps, measles, and EBV EBNA antibody were also equivalent in the three groups.

Several theoretical objections to immunizing patients have been studied and dismissed. First, vaccination of rheumatology patients does not cause induction of autoantibodies. Second, immunizations are not associated with exacerbations of disease. Finally, there are no contraindications to immunization based on RA disease activity (by lab or clinical measures), by the use of most oral DMARDs including prednisone and cyclosporin-A, by patient gender, and by patient age (35-40).

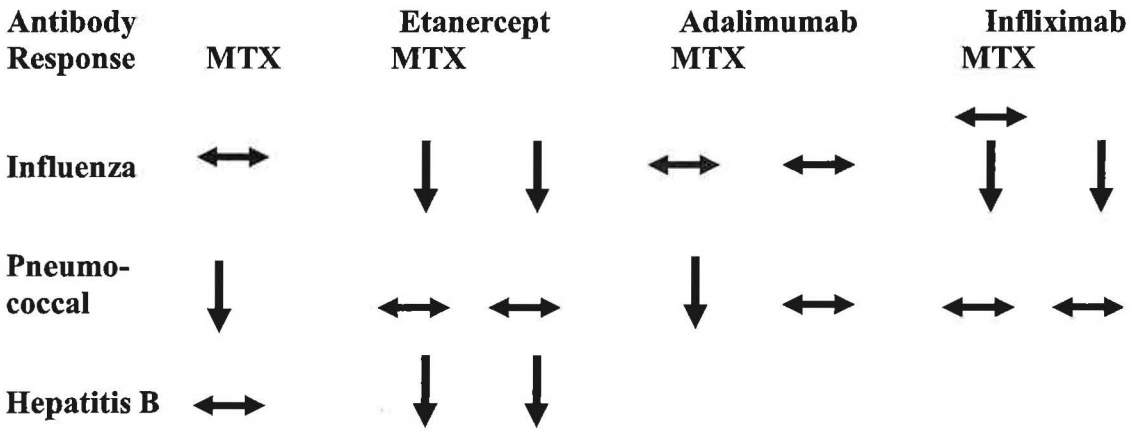

Table 3. Antibody response to immunization in the presence of selected anti-TNFα medications with and without methotrexate. Responses are listed as either unchanged ↔ or decreased ↓ .

Recommendations:

1. Immunize all patients with inflammatory rheumatic diseases such as RA.
2. For those who do not achieve protective titers, consider a switch from etanercept or infliximab to adalimumab (unstudied if this is effective).
3. Or, consider pausing the biologic for a short period (unstudied if effective or how long the interruption in therapy should be).

Varicella Zoster virus and the Zostavax vaccine.

Varicella zoster virus (VZV) becomes a latent virus in dorsal root ganglia after natural infection or vaccination. Reactivation, commonly referred to as shingles, can occur with a decrease in cell-mediated immunity by T-lymphocytes. (By contrast, control of varicella infection relies significantly on humoral immunity, a B-lymphocyte function). Up to 1 million Americans per year experience an outbreak of shingles. Serious complications of VZV include orbital involvement (herpes zoster ophthalmicus, seen in 10-25% of cases) and post-herpetic neuralgia (in 10-18% of cases) (41).

Immunosuppression, whether from disease or from medications, is a recognized risk factor for HZV reactivation. As shown in Table 4 below, the incidence of shingles increases in those over age 60, but also in those with inflammatory disease such as systemic lupus erythematosus, rheumatoid arthritis, or Wegener's granulomatosis. Cyclophosphamide, azathioprine, and prednisone over 20 mg/d are rheumatologic medications associated with immunosuppression and shingles risk (42, 43). The immunosuppressed are at risk of more severe rash, visceral dissemination, and death.

Patients	Cases per 1000 patient-years
US population	3 to 4
Age > 60	10
SLE	15 to 91
RA	10 to 15
Wegener's granulomatosis	45

Table 4. Incidence of zoster in rheumatology patients.

Recently, there was a report of the zoster incidence in RA patients on biologics participating in the German Biologics Register RABBIT (44). Demographics were typical of the larger trials in RA: mean age 54 years, 75% female, and 80% positive for rheumatoid factor. During the observation period 2001 to 2006, there were 86 cases of zoster in 82 patients. 39 cases occurred in patients on anti- TNFα monoclonal antibodies (adalimumab or infliximab), 23 in those taking etanercept, and 24 in those taking conventional DMARDs. The rate of zoster per 1000 patient-years was significantly lower in patients on conventional DMARDs (Table 5). The risk factors for zoster in this study additionally included older age and prednisone use, as has been described previously.

Drug	Zoster cases	Rate/1000 pt yrs	Hazard Ratio
Adalimumab Infliximab	39	11.1	1.82 *
Etanercept	23	8.9	1.36
All anti-TNFα	62	10.1	1.63
DMARD	24	5.6	1.00

Table 5: Incidence rate of zoster and hazard ratio in rheumatoid arthritis patients in the RABBIT registry on anti-TNFα medication or traditional oral medication (DMARD).
* statistically significant

A second recent study of zoster in RA was performed in US veterans (45). 20,357 veterans, mean age 58.5 years, with rheumatoid arthritis were divided into three categories:

- Group 1: mild disease (treated with hydroxychloroquine, sulfasalazine, auranofin, IM gold, penicillamine)
- Group 2: moderate disease (treated with methotrexate, leflunomide, azathioprine, cyclophosphamide, cyclosporine, anakinra)
- Group 3: severe disease (treated with TNFα antagonists)

The results showed that there were 713 episodes of Zoster (9.96/1000 pt-yrs). This rate was 2 to 5 fold higher than general population. The risks for zoster in this study were older age, malignancy, chronic lung disease, kidney disease, liver disease, and prednisone use. The rates of zoster were significantly lower in group 1 compared to the other two:

- Group 2 vs. Group 1: Rate 11.18 vs. 8.00/1000 pt-yrs ($p<0.001$)
- Group 3 vs. Group 1: Rate 10.60 vs. 8.00/1000 pt-yrs ($p<0.001$)

Figure 3 shows that zoster-free survival diverged in Group1 versus Groups 2 and 3 after year 2 of the study.

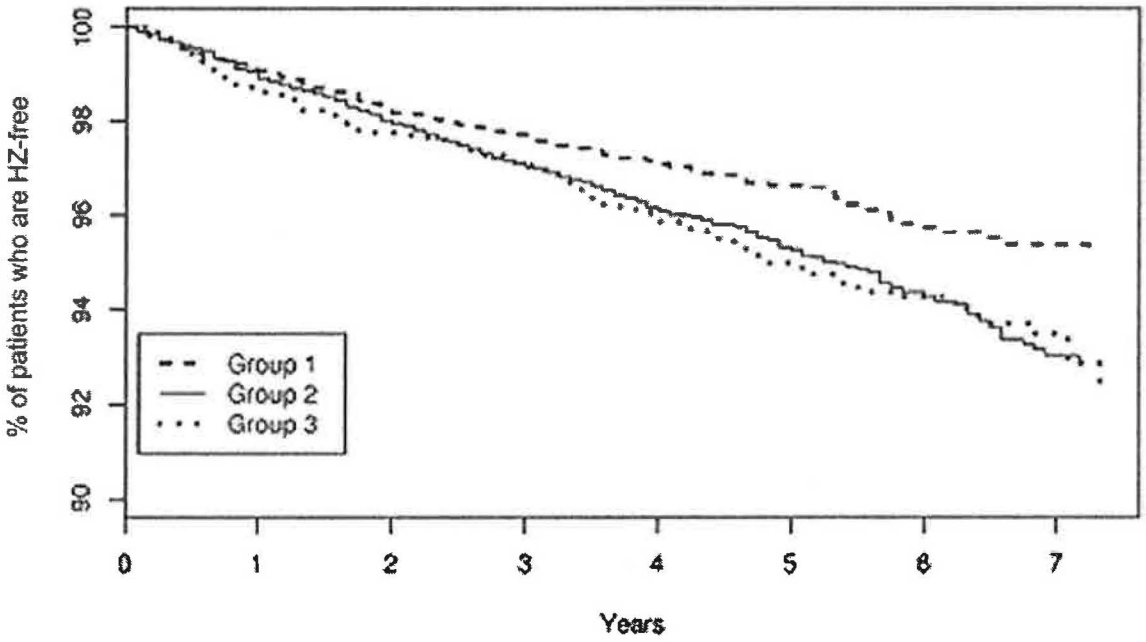

Figure 3. Years of zoster-free survival among veterans receiving different RA therapies.

Since 2005 a Zoster vaccine, Zostavax, has been available. It is a live attenuated virus indicated for immunocompetent individuals over age 60. The vaccine is given as a single subcutaneous dose in the upper arm and costs about $150. Studies in 38,546 persons showed a reduction in incidence of shingles by 51% and a reduction of post-herpetic neuralgia by 67%. According to the package insert, the vaccine is contraindicated for persons with acute zoster or postherpetic neuralgia, with primary or acquired immunodeficiency, those on immunosuppressive medications, and in pregnant women.

Studies are currently lacking on the drugs and specific doses that are sufficiently immunosuppressive to warrant avoidance of the Zoster vaccine. The ACR Taskforce Panel, a group of experts, recommended that Zostavax not be used for patients taking biologic medications in general (46). The CDC Advisory Committee on Immunization Practices considered several specific situations and recommended avoidance of Zostavax in those with malignancy in the bone marrow or lymphatics, patients with hematologic stem cell transplant, patients with HIV or AIDS, and those with cellular (but not humoral) immunodeficiency (42). The then-available TNFα antagonists, adalimumab, infliximab, and etanercept, were specifically mentioned as contraindications. On the other hand, older rheumatologic medications such as prednisone (under 20 mg/d, or any dose for less than 2 weeks), methotrexate $\leq$0.4 mg/kg/week, or azathioprine $\leq$3 mg/kg/day were not felt to be contraindications to successful vaccination. The suggested strategy was to vaccinate at least 14 days prior to initiation of immunosuppressive therapies.

Conclusions for use of Zostavax in rheumatoid arthritis.

1. There is an elevated risk of zoster in RA patients, and further elevation may be seen due to patient age over 60 and use of immunosuppressive treatment regimens.
2. For patients over age 60, Zostavax should be given even in the face of low dose prednisone, methotrexate, and likely all other oral DMARDs.
3. Zostavax, a live vaccine, is not recommended for patients on biologics (the five TNFα antagonists, anakinra, abatacept, rituximab).
4. Providers should plan vaccination at least 2 weeks before starting a biologic. There is no information on pausing use of a biologic in order to vaccinate.
5. There are insufficient data on RA patients under age 60, and patients with other rheumatic diseases.

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