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Hotline

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Herpes Zoster (Shingles) Vaccine Guidelines for Immunosuppressed Patients

On June 6, 2008, the CDC Advisory Committee on Immunization Practices issued recommendations for the prevention of herpes zoster, with new directives important for rheumatic disease patients receiving immunosuppressive therapy. This *Hotline* will review these and other guidelines for zoster vaccine use.

Shingles (H. zoster) affects nearly 1 million Americans annually (incidence of 3-4/1000 pt-yrs) and will affect 1 in 3 adults during their lifetime. Early in life, following natural infection (i.e., chickenpox) or vaccination, latent varicella zoster virus (VZV) takes up residence in the dorsal root ganglia and over time, reactivation may occur under varied circumstances, including alterations in cell-mediated immunity. Shingles may be complicated by H. zoster ophthalmicus (10-25%) and post-herpetic neuralgia (PHN; 10-18%). Prevention is desirable, especially in immunosuppressed patients who are at greater risk for m ore severe rashes, visceral dissemination or death. The incidence of shingles increases with: advancing age (age > 60 yrs - 10 cases/1000 pt-yrs); immunosuppression from cancer, transplantation, autoimmunity (SLE 15-91 cases/1000 pt-yrs; RA 10-15 cases/100 pt-yrs; Wegener's 45 cases/1000 pr-yrs[4,5]); and certain immunosuppressive agents (e.g., cyclophosphamide, azathioprine, high dose prednisone). A contributory role for methotrexate or biologic therapies in VZV infection or reactivation has not been established.

The Vaccine. A lyophilized, live, attenuated zoster vaccine (Zostavax®) has been available since 2006 for use in immunocompetant persons aged > 60 yrs. Of note, the adult vaccine uses the same strain of virus as the pediatric vaccine (Varivax®) but is at least 14 times more potent. The vaccine was studied for three years in 38,546 individuals > 60 years with a 51% reduction in shingles and a 67% reduction in PHN. The vaccine has not been studied in immunosuppressed patients – nonetheless, existing guidelines warn against its use in the immunosuppressed or those on immunosuppressive therapy. The vaccine is given as a single subcutaneous injection in the upper arm. Side effects include injection site reactions (common) and headache (uncommon). Vaccination rarely induces acute VZV infection. The approximate cost of vaccine is $150 (U.S.).

Recommendations for the use of the Zoster Vaccine

Manufacturer's (Merck) Package Insert[2]: Zoster Vaccine Live is indicated for the prevention of shingles in person's age > 60 years. It is contraindicated in the treatment of acute zoster or PHN, those with anaphylactic/anaphylactoid reactions to gelatin, neomycin, any vaccine components, those with a history of primary or acquired immunodeficiency, those on immunosuppressives and women of child-bearing age or who are pregnant.
American College of Physicians Guidelines[1]: Shingles vaccine is indicated for adults aged > 60 years. It is contraindicated in those with life-threatening allergic reactions to gelatin, neomycin, any component of shingles vaccine, or the immunosuppressed (HIV+, AIDS, lymphoma, leukemia, neoplasia affecting the bone marrow), those on immunosuppressives, patients with active/untreated tuberculosis and pregnancy. Patients with URI, bronchitis may receive the vaccine, however it should be avoided in those with more serious infections or fever $\geq$ 101°F.

ACR (in Guidelines for the Treatment of RA)[3]: In June 2008, the ACR Guidelines Taskforce Panel recommended that patients with RA receiving leflunomide, methotrexate or sulfasalazine can be immunized with inactive viral vaccines (e.g., influenza and pneumococcal) in accordance with CDC recommendations. They recommended avoidance of live viral vaccine preparations (e.g., Zostavax) with "all biologic agents", but provide no directives on whether live vaccines are safe with MTX or corticosteroid use.

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CDC Advisory Committee on Immunization Practices Recommendations[4]: Zoster vaccination is indicated in all immunocompetent persons > 60 yrs of age, including patients with a previous episode of zoster or chronic medical conditions, provided they have no contraindications. Zoster vaccination is not indicated for the treatment of acute zoster or PHN. Patients who may become immunosuppressed due to disease or drugs should receive vaccination at the first clinical encounter, at least 14 days before "anticipated immunosuppression" or immunosuppressive therapy.

The ACIP guidelines are novel in that they recommend vaccination of patients with inflammatory disorders who are receiving prednisone ≤ 20 mg/day, short term (< 2 weeks) corticosteroids, topical or intra-articular corticosteroids, 'low dose' methotrexate (defined as ≤ 0.4 mg/kg/week), azathioprine (≤3.0 mg/kg/day) or 6-mercaptopurine (≤1.5 mg/kg/day). The guidelines do not address vaccine use when these agents are combined. However, they state the vaccine should *not* be given in the following circumstances:

- Recombinant human immune mediators (specifically naming adalimumab, infliximab and etanercept);
- Active leukemia, lymphoma, malignant neoplasm's affecting bone marrow or lymphatics;
- AIDS/HIV patients and those with CD4 lymphocyte counts ≤ 200 per mm^3;
- High dose corticosteroids ≥ 20 mg/day for more than two weeks;
- Clinical or laboratory evidence of cellular immunodeficiency (patients with hypogammaglobulinemia or dysgammaglobulinemia can receive the zoster vaccine)
- Hematopoetic stem cell transplantation.
- Pregnancy
- Severe acute illness

These recommendations are expert-opinion based, as there are no studies or safety data to support these guidelines. Moreover the authors fail to note the risk of immunosuppression attributable to the active inflammatory disorder itself.

The Bottom Line:

- RA and its therapies may put older patients at risk for shingles; because of their immunosuppressed status, these patients are at greater risk of developing H. zoster and having more severe outcomes.
- Based on these new CDC ACIP recommendations, rheumatologists should consider giving zoster vaccine to **all** RA patients 60 years of age and older, even if they are on MTX and low-dose prednisone (especially since many RA patients may ultimately receive biologic agents).
- Until more research becomes available it is still advisable to avoid the zoster vaccine in patients actively receiving TNF inhibitors, as well as abatacept, rituximab and anakinra. In some, it may be advisable to delay the initiation of biologic therapy until at least two weeks after the zoster vaccine is given.
- Patients who experience side effects or toxicity related to this vaccine should be reported to the FDA at www.Medwatch.com

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