15 SEPTEMBER

Stan Deresinski, Section Editor

In the Literature

Rituximab and Progressive Multifocal Leukoencephalopathy (PML)

Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy following rituximab therapy in HIV negative patients: a report of 57 cases from the Research on Adverse Event and Reports (RADAR) project. Blood 2009; 113: 4834–40.

PML results from reactivation of latent JC virus infection in the brain and usually occurs in severely immunocompromised patients, although the disease has also been reported in some apparently immunocompetent individuals. The development of numerous cases in patients receiving natalizumab (Tysabri; Elan), a monoclonal antibody targeting α-4-integrin, seemed initially surprising, but the association of this drug with the development of PML subsequently became unequivocal. The use of efalizumab (Raptiva; Genetech), an anti-CD11a (LFA-1) monoclonal antibody, has also been associated with the development of a small number of cases of PML, leading to its recent voluntary removal from the US market. Rituximab is a monoclonal antibody directed against CD20, a marker present on >95% of B lymphocytes, that is receiving increasingly wide use for B cell malignancies and some immunologic diseases. Individual case reports of PML in patients receiving rituximab have led to a closer examination of a possible association between the 2.

The RADAR project, a collaborative, multicenter effort tracking adverse drug events, identified 57 rituximab recipients reported to have developed PML during the period from 1997 to 2008. These included 52 persons with lymphoproliferative disorders, 2 with systemic lupus erythematosus, and 1 each with rheumatoid arthritis, idiopathic autoimmune pancytopenia, and immune thrombocytopenia. The patients had received a median of 6 doses of rituximab (range, 1–28 doses). The median interval from the first dose to the diagnosis of PML was 16 months (range, 1–90 months), and the median interval from last dose to diagnosis was 5.5 months (range, 0.3–66 months). All patients had potential reasons for immunosuppression in addition to receipt of rituximab. Seven had undergone hematopoietic stem cell transplantation, and 26 and 39 had received purine analogues and/or alkylating agents, respectively. Almost 80% had receive corticosteroids at some time.

The interaction of rituximab with CD20 leads to complement-mediated and antibody-dependent cytotoxicity with rapid B cell depletion. Hypogammablobulinemia develops in a minority of patients. Full B cell recovery takes months to years. The potential contribution of rituximab to the development of PML is difficult to determine from this analysis, in large part because of the complex treatment history of most of the patients. Some reports have suggested an increased risk of a variety of viral infections after rituximab therapy. A recent meta-analysis found that rituximab therapy for lymphoma was associated with significantly increased risks of neutropenia and infection, although this was not uniformly seen in all the trials evaluated. Thus, the precise role of rituximab as a proximate factor in the development of opportunistic infections, including reactivation of JC virus infection, remains to be definitively determined.

USA 300: Virulence at the Core

Li M, Diep BA, Villaruz AE, et al. Evolution of virulence in epidemic community-associated methicillin-resistant *Staphylococcus aureus.* Proc Natl Acad Sci U S A 2009; 106:5883–8.

Approximately 30% of the genetic material carried by *Staphylococcus aureus* is located in the "accessory" genome—DNA that has been horizontally acquired and that is not a part of the core species-defining genome. In *S. aureus,* the mobile genetic elements constituting this large accessory genome include such genes as that which encodes the Panton-Valentine leukocidin (PVL) and which have been suggested to be responsible for virulence. The role of elements such as PVL, which is present in almost all USA300 strains of methicillin-resistant *S. aureus,* the dominant community-acquired strain in the United States, in the virulence of *S. aureus* has been strongly questioned. Li and colleagues examined this question by investigating the evolution of virulence in USA300 relative to its progenitor strain, USA500, and to other members of clonal complex 8 from which they arose.

The investigators determined that USA500, in contrast to USA300, contained none of the known enterotoxin gene usually encoded on prophages and pathogenicity islands (which are the source of much of the accessory genome). USA300, however, acquired multiple mobile genetic elements encoding virulence factors after its evolution from USA500; these included coding elements for the arginine catabolic mobile element, some enterotoxins, and PVL. Despite the absence of these factors in USA500, the 2 strains had equivalent virulence in murine models of bacteremia and skin infection, and both were more virulent than other strains belonging to clonal complex 8. USA300 and USA500 each demonstrated evidence of a greater ability than other strains to evade the innate immune response, including lysis of neutrophils and resistance to cationic proteins. USA300 and USA500 also had higher expression of α-toxin and α-type phenol-soluble modulins (the marked ability to lyse neutrophils was largely the result of the latter)—2 elements previously reported to play a key role in the virulence of *S. aureus.* Other experiments confirmed previous findings that the

global virulence regulator *agr* plays a major role in the virulence of USA300 and USA500, other regulatory influences are also important.

Thus, the horizontal acquisition of MBEs, including those encoding elements such as enterotoxins and PVL, play only a limited role in the virulence of USA300. In contrast, the expression of elements of the core genome, such as phenol-soluble modulins and α-toxin, is important in accounting for this virulence. This suggests that differences in virulence are not largely the result of the presence or absence of individual mobile genetic elements of the accessory genome, but rather a function of the differential expression of elements of the core genome of *S. aureus*. This suggests also that experimental vaccines and therapies aimed only at accessory gene elements may prove to be ineffective and that core factors, including regulatory elements, may prove to be more productive targets.

Combination Therapy of Neurocysticercosis

Kaur S, Singhi P, Singhi S, Khandelwal N. Combination therapy with albendazole and praziquantel versus albendazole alone in children with seizures and single lesion neurocysticercosis: a randomized, placebo-controlled double blind trial. Pediatr Infect Dis J 2009; 28:403–6.

Kaur and colleagues in Chandigarh, India, randomized children with single parenchyhymal neurocysticercosis lesions to treatment with either albendazole plus placebo or albendazole plus praziquantel in a blinded fashion. Albendazole was given at a dosage of 5 mg/kg 3 times per day for 7 days, whereas praziquantel was given as three 25-mg/kg doses in 1 day. Both groups received prednisolone at a daily dose of 2 mg/kg for the 5 days. All patients had generalized or focal seizures for <3 months and a single characteristic brain lesion <20 mm in diameter with contrast enhancement. None had previously been treated. All patients received medication, most often carbamazepine, to prevent seizures. No mention is made regarding monitoring serum concentrations of these drugs.

Fifty patients received albendazole alone, and 53 received the combination. Complete lesion resolution in the monotherapy group at 1, 3, and 6 months was observed in 25%, 42%, and 52% of patients, respectively, whereas in the combination therapy group, it was seen in 35%, 60%, and 72%, respectively. Although the results were numerically superior in the combination arm, this difference did not achieve statistical significance. Seizure recurrence occurred in 3 patients in each group. Treatment in each group was well tolerated.

An important problem with this trial is the apparent lack of monitoring of the serum concentrations of the anti-seizure medications. Optimal dosing based on serum concentrations of these drugs is the most important determinant of seizure recurrence [1]. The authors indicate that a sample size calculation was made, but they do not indicate the criteria used for that calculation and do not state the power of the study. However, there was an apparent nonsignificant trend in lesion resolution favoring combination therapy. Whether this matters, however, is another story, because it is unclear that faster lesion resolution is clinically important.

Reference

1. White AC Jr. New developments in the management of neurocysticercosis. J Infect Dis **2009**; 199:1261–2.

DOI: 10.1086/600118