Combination Antiretroviral Therapy with Tenofovir, Emtricitabine or Lamivudine, and Nevirapine

To the Editor—Lapadula et al. [1] have reported that regimens consisting of tenofovir, emtricitabine, and nevirapine are associated with a risk of early virologic failure in antiretroviral-naive, HIV-infected patients. This conclusion was based on the interim results of a small, premature stopped trial in which 3 of the 7 patients who received this regimen experienced an increase in HIV RNA levels at 12 weeks, after an initial decrease at 4 weeks. This interim analysis was prompted by data showing early virologic failure in antiretroviral-naive, HIV-infected patients. The results from Lapadula et al. [1] and from the DAUFIN study [2] are in contrast with the high rates of virologic suppression (≥80%) observed at 2 years with nevirapine-based regimens in >800 treatment-naive patients from the HIV/AIDS Therapy Evaluation in the Netherlands cohort and the Swiss HIV Cohort Study [6]. Other recent studies have shown virologic suppression for up to 48 weeks in patients taking nevirapine combined with tenofovir and emtricitabine or lamivudine [7–9]. As a consequence of increased recognition of thymidine analog toxicity, a regimen comprising tenofovir, either emtricitabine or lamivudine, and nevirapine is now more commonly used in treatment programs in resource-constrained settings. Our own international experience has shown that this regimen results in viral suppression rates of ≥75% at 12 months or later. This combination continues to be a common component of global HIV/AIDS programs, and it has a number of advantages that support its widespread use. It has an excellent long-term toxicity profile [10], and it is appropriate to use in a wide population of patients, including female patients of reproductive age. Larger prospective studies (Nevirapine vs. Atazanavir Boosted with Ritonavir on a Background of Truvada in HIV-Infected Naive Patients [NEwArT] and Atazanavir/Ritonavir on a Background of Tenofovir and Emtricitabine vs. Nevirapine [ArTEN]) are under way, to more definitively evaluate such regimens. The independent Virology Data and Safety Monitoring Board review of the ArTEN trial status on 10 March 2008, which included data for 283 patients at up to 48 weeks after initiation of therapy, recommended that this trial continue as designed. The available evidence does not support changing our current use of tenofovir plus emtricitabine (or lamivudine) and nevirapine to treat antiretroviral-naive patients.

Acknowledgments

Financial support. Boehringer Ingelheim Pharmaceuticals.

Manuscript preparation. Insight Medical Communications provided assistance in preparing and editing the letter.

Potential conflicts of interest. Within the past 2 years, R.R.R. has received research contracts and grants from Abbott, Boehringer Ingelheim, Gilead, Merck, Pfizer, Progenics, and Schering and has served on speakers’ bureaus for Abbott, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Merck, and Pfizer. J.S.M. is an employee of Boehringer Ingelheim Pharmaceuticals.

Robert R. Redfield1 and J. Scott Morrow2

1Institute of Human Virology, University of Maryland, Baltimore; and 2Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut

References


4. Davis C, Gilliam B, Amoroso A, et al. Lack of pharmacokinetic (PK) interaction of tenofovir (TDF) and emtricitabine (FTC) on nevirapine


Correspondence—We read with interest the recent article by Rubinstein et al. [1] in Clinical Infectious Diseases. We would like to comment on the statement “In France in 2002, Gillet et al. [2] described 16 cases of CAP [community-acquired pneumonia] caused by CA-MRSA [community-acquired methicillin-resistant Staphylococcus aureus] containing SCCmec type IV, as well as the gene encoding Panton-Valentine leukocidin (PVL), a toxin that destroys polymorphonuclear leukocytes. The patients were young (median age, 14.8 years), the pneumonia was frequently preceded by an influenza-like illness, the disease course was stormy, and the 48-h survival rate was 63% (figure 1). The lethal potential of this postinfluenza pneumonia was confirmed in the United States” [1, p. S378]. Everything stated is in accordance with an article in The Lancet that we coauthored [2], except that most of the strains in this study were not CA-MRSA strains; only 1 of the 16 cases was caused by MRSA. Similarly, in another paragraph, Rubinstein et al. [1] stated that “Pneumonia in young, previously healthy adults with a preceding influenza-like illness characterized by severe respiratory symptoms, hemoptysis, high fever, leukopenia…should lead one to suspect CA-MRSA infection” [1, p. S379]. This clinical description completely corresponds to that of necrotizing pneumonia, regardless of resistance to methicillin, as described in the article that we coauthored [2] and confirmed in a recent analysis of a series of 50 unrelated cases of necrotizing pneumonia collected worldwide. In this recent series, MRSA was involved in only 12% of cases [3]. We understand that, in the United States, the high prevalence of CA-MRSA USA300, which harbors the PVL genes, overshadows the fact that, in other countries, the vast majority of cases of highly severe pneumonia are caused by PVL-positive methicillin-susceptible S. aureus. Some case reports from the United States describe typical necrotizing pneumonia caused by PVL-positive methicillin-susceptible S. aureus [4, 5]. In our opinion, the confusion between CA-MRSA and PVL is also a reason for the current controversy about the role of PVL in disease and the ongoing spread of CA-MRSA USA300. We agree with other reports that the epidemic success of MRSA USA300 is likely attributable to other features that are specific to this strain, such as the presence of a full-length arginine catabolic mobile element [6]; the current European CA-MRSA clone ST80, which is significantly less prevalent in Europe than USA300 is in the United States, harbors PVL but not the arginine catabolic mobile element. With regard to necrotizing pneumonia, which remains an infrequently occurring syndrome, epidemiological and experimental data argue for an important role of PVL in the severity of this disease [2, 4, 5, 7–9]. This probably requires additional investigation; meanwhile, we think it is reasonable to take toxin production into account in the therapeutic management of necrotizing pneumonia, whether the strain is susceptible or resistant to methicillin. In the case of resistance to methicillin, this is consistent with the remark by Rubinstein et al. [1] that “Although it has not been established that the combination of a bactericidal agent with a toxic-suppressing agent, such as clindamycin or linezolid, is associated with improved outcome, it is the general impression of experienced clinicians that vancomycin should not be used as a single agent for the treatment of CA-MRSA pneumonia” [1, p. S382]. In our opinion, this attitude should be extended to cases of necrotizing pneumonia due to community-acquired methicillin-susceptible S. aureus, for which we consider it to be reasonable to combine β-lactams with a toxin-suppressing agent for treatment.

Reprints or correspondence: Dr. Robert R. Redfield, Institute of Human Virology, University of Maryland, Baltimore, 725 W. Lombard St., Baltimore, MD 21201 (rredfield@ihv.umd.edu).

Clinical Infectious Diseases 2008;47:984–5 © 2008 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2008/4707-0024$15.00 DOI: 10.1086/591802

Association of Necrotizing Pneumonia with Panton-Valentine Leukocidin–Producing Staphylococcus aureus, Regardless of Methicillin Resistance

To the Editor—We read with interest the recent article by Rubinstein et al. [1] in Clinical Infectious Diseases. We would like to comment on the statement “In France in 2002, Gillet et al. [2] described 16 cases of CAP [community-acquired pneumonia] caused by CA-MRSA [community-acquired methicillin-resistant Staphylococcus aureus] containing SCCmec type IV, as well as the gene encoding Panton-Valentine leukocidin (PVL), a toxin that destroys polymorphonuclear leukocytes. The patients were young (median age, 14.8 years), the pneumonia was frequently preceded by an influenza-like illness, the disease course was stormy, and the 48-h survival rate was 63% (figure 1). The lethal potential of this postinfluenza pneumonia was confirmed in the United States” [1, p. S378]. Everything stated is in accordance with an article in The Lancet that we coauthored [2], except that most of the strains in this study were not CA-MRSA strains; only 1 of the 16 cases was caused by MRSA. Similarly, in another paragraph, Rubinstein et al. [1] stated that “Pneumonia in young, previously healthy adults with a preceding influenza-like illness characterized by severe respiratory symptoms, hemoptysis, high fever, leukopenia…should lead one to suspect CA-MRSA infection” [1, p. S379]. This clinical description completely corresponds to that of necrotizing pneumonia, regardless of resistance to methicillin, as described in the article that we coauthored [2] and confirmed in a recent analysis of a series of 50 unrelated cases of necrotizing pneumonia collected worldwide. In this recent series, MRSA was involved in only 12% of cases [3]. We understand that, in the United States, the high prevalence of CA-MRSA USA300, which harbors the PVL genes, overshadows the fact that, in other countries, the vast majority of cases of highly severe pneumonia are caused by PVL-positive methicillin-susceptible S. aureus. Some case reports from the United States describe typical necrotizing pneumonia caused by PVL-positive methicillin-susceptible S. aureus [4, 5]. In our opinion, the confusion between CA-MRSA and PVL is also a reason for the current controversy about the role of PVL in disease and the ongoing spread of CA-MRSA USA300. We agree with other reports that the epidemic success of MRSA USA300 is likely attributable to other features that are specific to this strain, such as the presence of a full-length arginine catabolic mobile element [6]; the current European CA-MRSA clone ST80, which is significantly less prevalent in Europe than USA300 is in the United States, harbors PVL but not the arginine catabolic mobile element. With regard to necrotizing pneumonia, which remains an infrequently occurring syndrome, epidemiological and experimental data argue for an important role of PVL in the severity of this disease [2, 4, 5, 7–9]. This probably requires additional investigation; meanwhile, we think it is reasonable to take toxin production into account in the therapeutic management of necrotizing pneumonia, whether the strain is susceptible or resistant to methicillin. In the case of resistance to methicillin, this is consistent with the remark by Rubinstein et al. [1] that “Although it has not been established that the combination of a bactericidal agent with a toxic-suppressing agent, such as clindamycin or linezolid, is associated with improved outcome, it is the general impression of experienced clinicians that vancomycin should not be used as a single agent for the treatment of CA-MRSA pneumonia” [1, p. S382]. In our opinion, this attitude should be extended to cases of necrotizing pneumonia due to community-acquired methicillin-susceptible S. aureus, for which we consider it to be reasonable to combine β-lactams with a toxin-suppressing agent for treatment.