from western Balkan countries into Germany (6).

The costs associated with such introductions are numerous. These costs include the diagnostic investigation of suspected cases, particularly if molecular analysis is required to confirm the source of the incursion, as was required when rabies was detected in a puppy in Switzerland (7).

Subsequent investigations to identify animal and human contact cases, often requiring >1 national or international agency, are needed to ensure that the disease has not spread and potential human contacts receive appropriate postexposure prophylaxis. In some cases the implementation of hotlines and several press releases was necessary to cope with the demand for information by the public (4). However, although media attention in such cases reached its primary and immediate objective, i.e., no secondary human rabies cases were reported, it may also have contributed to enhancing the sense of rabies risk, thereby prompting persons to associate dog bites in general with rabies and thus leading to increased numbers of persons seeking postexposure prophylaxis unnecessarily for several months (8). Further costs are also incurred in the euthanasia or quarantine of contact animals.

The evidence suggests that this trend for importation of animals incubating rabies will continue, requiring member states to maintain vigilance with measures appropriate to the potential risk and consequences of a rabies outbreak. This vigilance should involve rapid investigation of suspected cases of disease, maintenance of rabies diagnostic capacity and contingency plans, and improved coordination between member states to deal with disease introduction.

This study was supported by Defra grant SV3500.

**Nicholas Johnson, Conrad Freuling, Daniel Horton, Thomas Müller, and Anthony R. Fooks**

**Author affiliations:** Veterinary Laboratories Agency–Weybridge, Woodham Lane, UK (N. Johnson, D. Horton, A.R. Fooks); and Friedrich-Loeffler-Institute, Wusterhausen, Germany (C. Freuling, T. Müller)

DOI: 10.3201/eid1704.101154

**References**

1. De Benedictis P, Gallo T, Lob A, Coassin R, Squecco G, Ferri G, et al. Emergence of fox rabies in north-eastern Italy. Eurosurveill. 2008;13(45):pii:19033.

2. Bruyère-Masson V, Barrat J, Cliquet F, Rotivel Y, Bourhy H, Brie P, et al. A puppy illegally imported from Morocco brings rabies to France. Rabies Bulletin Europe. 2001;25.3:12–3.

3. French Multidisciplinary Investigation Teams. Identification of a rabid dog in France illegally introduced from Morocco. Eurosurveill. 2003;13(11):pii:8066.

4. Servas V, Mailles A, Neau D, Castor C, Manetti A, Fouquet E, et al. An imported case of canine rabies in Aquitaine: investigation and management of the contacts at risk, August 2004–March 2005. Eurosurveill. 2005;10(11):pii=578.

5. Sánchez Serrano LP, Abellán García C. The new face of rabies in Spain: infection through insectivorous bats, 1987–2002. Eurosurveill. 2003;7(27):pii=2250.

6. Weiss B, Hoffmann U, Freuling C, Müller T, Fesseler M, Renner C. Rabies exposure due to an illegally imported dog in Germany. Rabies Bulletin Europe. 2009;33.2:5–7.

7. Zanoni R, Breitenmoser U. Rabies in a puppy in Nyon, Switzerland. Rabies Bulletin Europe. 2003;27.3:5–7.

8. Lardon Z, Watier L, Brunet A, Bernède C, Goudal M, Dacheux L, et al. Imported epidemic rabies increases patient demand for and physician delivery of antirabies prophylaxis. PLoS Negl Trop Dis. 2010;4:e723. DOI: 10.1371/journal.pntd.0000723

Address for correspondence: Nicholas Johnson, Rabies and Wildlife Zoonoses Group, Veterinary Laboratories Agency–Weybridge, Woodham Lane, Surrey, KT15 3NB, UK; email: n.johnson2@vla.defra.gsi.gov.uk

---

**Cytomegalovirus Viremia, Pneumonitis, and Tocilizumab Therapy**

To the Editor: Tocilizumab is a monoclonal antibody that competitively inhibits binding of interleukin-6 (IL-6) to its receptor. It is approved for treatment of rheumatoid arthritis (RA) as monotherapy or with methotrexate. We report a case of cytomegalovirus (CMV) disease complicating treatment with an IL-6 receptor antagonist.

A 41-year-old man who had a diagnosis of nonerosive RA (seronegative for rheumatoid factor and anticyclic citrullinated peptide antibody) in 1994 had fevers in May 2010. Previous treatment included etanercept, methotrexate, and various doses of prednisone (highest dose 40 mg/day). Because of uncontrolled RA, he was treated with monthly infusions of tocilizumab, 600 mg (≈4 mg/kg, first infusion in March 2010 and the second in April 2010), methotrexate (7.5 mg/week), and prednisone (5 mg/day from April 2010 onwards).

Fever, a productive cough with white sputum, and wheezing developed ≈3 weeks after his second infusion of tocilizumab, which resulted in RA symptom resolution (Figure). Tapering of steroid treatment and levofloxacin resulted in some improvement. However, after 1 week, persistent fever led to hospitalization. Worsening shortness of breath, nausea, and vomiting developed. Results of computed tomography (CT) scans of the chest, abdomen, and pelvis were unremarkable. He was transferred to the Cleveland Clinic because of hypotension and intravenous dye–induced renal failure.

Daily fever (≤103°F), shortness of breath, nausea, and mild diarrhea persisted. After cultures were obtained, he received 1 g vancomycin,
3.375 g piperacillin/tazobactam, and 5 mg/kg lipid amphotericin B (empiric therapy). After a single dose of these drugs, antimicrobial drugs were withheld. Methotrexate and tocilizumab were also withheld. Prednisone (5 mg/day for his duration in the hospital and after discharge) was continued and resulted in resolution of RA symptoms.

Laboratory testing (reference ranges) showed leukocyte count 1,850 cells/μL, hematocrit 26.8%, platelet count 21,000 cells/μL, aspartate aminotransferase 56 U/L (5–50 U/L), alkaline phosphatase 164 U/L (40–150 U/L), and serum creatinine 3.15 mg/dL (0.7–1.4 mg/dL). Testing included negative serologic results for Bartonella species, Coxiella burnetii, Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis, hepatitis A, B, and C viruses, HIV, and parvovirus B19; negative PCR results for H. capsulatum and Legionella pneumophila antigens, influenza A/B viruses, respiratory syncytial virus, and human herpesvirus 6; no growth for routine fungal and mycobacterial blood cultures, urine cultures, and stool cultures; negative direct immunofluorescence results for adenovirus, parainfluenza viruses, and human metapneumovirus; and negative stool results for ova and parasites. A bone marrow biopsy did not show any abnormalities.

PCR showed CMV viremia (maximum value 50,413 copies/mL whole blood). A test result for immunoglobulin G against CMV was positive, indicating reactivation of latent infection. Epstein-Barr virus (EBV) viremia was low (1,821 copies/mL whole blood). Although the patient likely showed clinically irrelevant EBV shedding, fatal reactivation of EBV during tocilizumab therapy has been reported (1).

Results of CT scans of chest, sinuses, abdomen, and pelvis on admission at our institution were unremarkable. However, scanning of indium 111–labeled leukocytes 12 days after admission showed bilateral pneumonitis, and repeat chest CT showed interval development of ground glass opacities in the right upper lobe.

The patient was treated with intravenous ganciclovir for 10 days at doses adjusted for renal failure. Treatment was changed to oral valganciclovir, 900 mg 2×/d for 20 days, upon discharge. His symptoms gradually improved, and he had no fever after ≈7 days of treatment. His CMV DNA level decreased to 4,996 copies/mL after 3 days of therapy. A negative result for CMV DNA was observed 14 days after starting therapy. Thirty-five days after starting therapy, a CMV DNA test result remained negative, leukocyte count increased to 3,740 cells/μL, hematocrit to 32.3%, and platelet count to 194,000 cells/μL. These findings suggest that pancytopenia was likely secondary to CMV infection. Creatinine level returned to the reference range, and liver enzyme levels improved (aspartate aminotransferase 52 U/L, alanine aminotransferase 73 U/L). Cytopenia and liver toxicity are side effects of treatment with tocilizumab (2). His condition showed improvement at follow-up 35 days after starting therapy. He continued to receive prednisone (5 mg/day) and RA symptoms were controlled.

Similar to therapeutic blockade of tumor necrosis factor-α (TNF-α), tocilizumab has been associated with increased risk for infections. Several cases of CMV disease complicating TNF-α blockade, including pneumonia, have been reported (3). As in this patient, the effect of steroids on risk for infection often cannot be determined. Given the role of IL-6 in antiviral immunity, CMV reactivation in IL-6 blockade is not surprising (4). Frequent adverse events are upper respiratory tract infections, headache, nasopharyngitis, and gastrointestinal symptoms (4). Rates of serious infections were 5.3 infections/100 patient-years in placebo-treated patients and 3.9 infections/100 patient-years in patients treated with tocilizumab for 6 months (2). This rate was 7.2 infections/100 patient-years after 3 months of TNF-α.

Figure. Timeline of events for a 41-year-old man with rheumatoid arthritis. CMV, cytomegalovirus; IV, intravenous.
blockade (5). Other opportunistic infections that have been reported in clinical trials include *Pneumocystis jirovecii* pneumonia, herpes zoster, EBV hepatitis, tuberculosis, and asymptomatic *Mycobacterium avium–intracellulare* (6–10). Thus, CMV disease should be considered when patients receiving tocilizumab have febrile syndromes.

**David van Duin, Cyndee Miranda, and Elaine Husni**

Author affiliation: Cleveland Clinic, Cleveland, Ohio, USA

DOI: 10.3201/eid1704.101057

References

1. Nishimoto N, Yoshizaki K, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al. Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial. Arthritis Rheum. 2004;50:1761–9. DOI: 10.1002/art.20303

2. European Medicines Agency. Actemra (tocilizumab): summary of product characteristics, 2009 [cited 2009 Mar 23]. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000955/WC500054890.pdf

3. Kim SY, Solomon DH. Tumor necrosis factor blockade and the risk of viral infection. Nat Rev Rheumatol. 2010;6:165–74. DOI: 10.1038/nrrheum.2009.279

4. Ramshaw IA, Ramsay AJ, Karupiah G, Rolph MS, Mahalingam S, Ruby JC. Cytokines and immunity to viral infections. Immunol Rev. 1997;159:119–35. DOI: 10.1111/j.1600-065X.1997.tb01011.x

5. Dixon WG, Symmons DP, Lunt M, Watson KD, Hyrich KL, Silman AJ. Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. Arthritis Rheum. 2007;56:2896–904. DOI: 10.1002/art.22808

6. Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying anti-rheumatic drug therapy study. Arthritis Rheum. 2008;58:2968–80. DOI: 10.1002/art.23940

7. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet. 2008;371:987–97. DOI: 10.1016/S0140-6736(08)60453-5

8. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J. Long-term safety and efficacy of tocilizumab, an anti-IL-6 receptor monoclonal antibody, in monotherapy, in patients with rheumatoid arthritis (the STREAM study): evidence of safety and efficacy in a 5-year extension study. Ann Rheum Dis. 2009;68:1580–4. DOI: 10.1136/ard.2008.092866

9. Yokota S, Imagawa T, Mori M, Miyamae T, Aihara Y, Takei S, et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. Lancet. 2008;371:998–1006. DOI: 10.1016/S0140-6736(08)60454-7

10. Nishimoto N, Ito K, Takagi N. Safety and efficacy profiles of tocilizumab monotherapy in Japanese patients with rheumatoid arthritis: meta-analysis of six initial trials and five long-term extensions. Mod Rheumatol. 2010;20:222–32. DOI: 10.1007/s10165-010-0279-5

Address for correspondence: David van Duin, Department of Infectious Diseases, Mailcode G21, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195, USA; email: vanduud@ccf.org

---

**Concurrent Influenza and Shigellosis Outbreaks, Papua New Guinea, 2009**

**To the Editor:** A high case-fatality ratio has often been associated with outbreaks of a new influenza virus but is less commonly reported in association with seasonal influenza. Nevertheless, in developing countries, seasonal influenza has been associated with a high proportion of deaths, especially among remote populations. In Madagascar, seasonal influenza mortality rates of 2.5% have been reported (1), with even higher rates (15%) reported in Indonesia (2) and in the highlands of Papua New Guinea (9.5%) (3). High mortality rates during influenza outbreaks in the developing setting have been ascribed to a lack of access to antimicrobial drugs to treat cases of secondary pneumonia and lack of access to health care in general (1).

Diarrheal disease is a major cause of illness and death throughout the world, with diarrheal outbreaks causing a substantial proportion of deaths (4). Endemic shigellosis is responsible for ≈10% of all cases of diarrhea among children <5 years of age living in developing countries and up to 75% of diarrheal deaths (5,6). Although epidemic *Shigella dysenteriae* causes the most dramatic form of *Shigella* spp. infections in developing countries with high attack rates and mortality rates, approximately half of the *Shigella* spp. infections are caused by *Shigella* spp. Despite the endemicity of both influenza viruses and *Shigella* spp. in developing countries, data on their co-infection are lacking.

In mid-August 2009, an outbreak of bloody diarrhea and influenza-like illness (ILI) was reported to health authorities in Menyamya, a remote highland region of Morobe Province, with an estimated population of 10,000 persons. On August 28, an investigation was conducted to identify the cause and extent and to implement control measures.

Two sets of data were collected at the Hakwange Aid Post in Menyamya: 1) laboratory-investigated cases, 2) verbal autopsies. An additional dataset of clinical cases was subsequently collected from surrounding facilities in the district.

Rapid verbal autopsies were conducted by using standardized questionnaires. Bloody diarrhea was