design, methods and preliminary accrual results of the Canadian Cervical Cancer Screening Trial (CCCaST). Int J Cancer 2006; 119:615-23.
10. Naucler P, Ryd W, Törnberg S, et al. Human papillomavirus and Papanicolaou tests to screen for cervical cancer. N Engl J Med 2007;357:1589-97.
11. Noorani HZ, Brown A, Skidmore B, Stuart GCE. Liquid-based cytology and human papillomavirus testing in cervical cancer. Technology report no. 40. Ottawa: Canadian Coordinating Office for Health Technology Assessment, 2003.
12. Kitchener HC, Almonte M, Wheeler P, et al. HPV testing in routine cervical screening: cross sectional data from the ARTISTIC trial. Br J Cancer 2006;95:56-61.

Bell's Palsy — Is Glucocorticoid Treatment Enough?

Donald H. Gilden, M.D., and Kenneth L. Tyler, M.D.

Approximately a third of cases of acute peripheral facial weakness are caused by trauma, diabetes mellitus, hypertension, eclampsia, the Ramsay Hunt syndrome (facial palsy with zoster oticus caused by varicella–zoster virus), Lyme disease, sarcoidosis, Sjögren's syndrome, parotid gland tumors, and amyloidosis and may even be a complication of intranasal influenza vaccine.[1] The remaining two thirds of cases are idiopathic (Bell's palsy).

Bell's palsy occurs in 20 to 32 persons per 100,000 per year[2,3] and affects both sexes and all ages. Fortunately, most patients with Bell's palsy recover completely, but 20 to 30% may have permanent, disfiguring facial weakness or paralysis.[3,4] Besides the asymmetry evident from limited retraction of the muscles around the angle of the mouth on one side and an inability to close the eye (Fig. 1), there may be other permanent sequelae, such as synkinesia, hyperacusis, a loss of taste, and an inability to produce tears. It is this substantial minority of patients with Bell's palsy on whom early treatment is focused.

The rationale for early and aggressive treatment is based on long-standing observations by surgeons who have reported the presence of facial-nerve swelling during decompression operations in patients with Bell's palsy.[5] Edema may be secondary to ischemia[6] or inflammation, as evidenced by contrast enhancement of the facial nerve seen on magnetic resonance imaging 9 to 23 days after the onset of Bell's palsy.[7] For years, physicians have treated patients with Bell's palsy as early as possible with glucocorticoids. In addition, the detection of herpes simplex virus in the endoneurial fluid of patients with Bell's palsy[8] has led to the widespread use of antiviral agents along with glucocorticoids in the past decade, although the exact role of the virus in disease pathogenesis is unknown. Most, but not all, of the numerous studies that have compared glucocorticoid treatment with placebo in patients with Bell's palsy have shown significant improvement with glucocorticoids.[9] Glucocorticoids also appear to confer a greater benefit than acyclovir in these patients.[10] Although the collective data suggest that glucocorticoids decrease the incidence of permanent facial paralysis, whether antiviral therapy confers additional benefits has not been known.

In this issue of the *Journal*, Sullivan et al.[11] report on a large study involving the treatment of

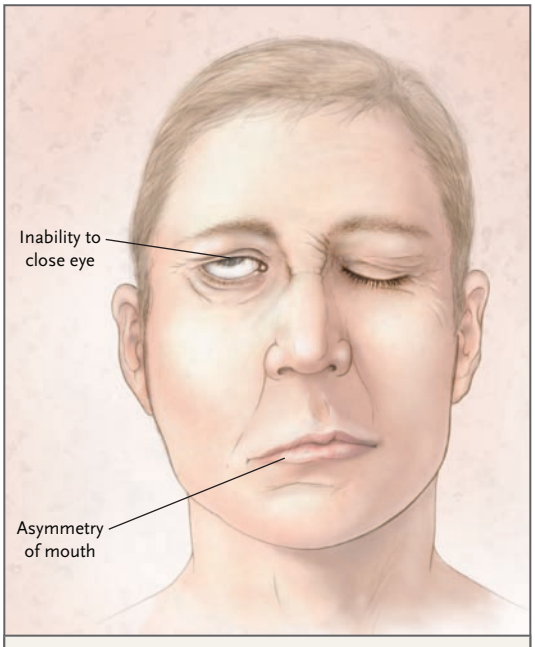

Figure 1. A Patient with Bell's Palsy Who Has Been Asked to Close His Eyes.
Typical signs include asymmetry from limited retraction of the muscles around the angle of the mouth and an inability to close one eye.

patients with Bell's palsy. The study was randomized, controlled, and double-blind, with predefined and specified outcome measures and follow-up for 9 months. Patients were recruited within 72 hours after the onset of symptoms from 17 hospitals in Scotland and were randomly assigned to treatment for 10 days with prednisolone, acyclovir, or both or with placebo. The House–Brackmann scale was used to assess recovery of facial function. Assessment of final outcomes at 9 months, which was possible in 496 patients, revealed complete facial-nerve recovery in 85.2% of patients who received placebo, supporting earlier reports in untreated patients.[12,13] Furthermore, 96.1% of patients who received prednisolone alone recovered completely, an absolute risk reduction of 11%, as compared with those receiving placebo alone. This absolute risk reduction means that 9 patients (95% confidence interval, 6 to 14) would need to be treated to achieve one additional full recovery.

Surprisingly, only 78.0% of patients who received acyclovir alone had recovered fully at 9 months, a proportion somewhat less than that after placebo treatment, and the percentage of patients who were completely recovered after treatment with a combination of acyclovir and prednisolone was slightly less (92.7%) than after treatment with prednisolone alone (96.1%). Overall, there was no evidence of benefit from acyclovir over placebo or from the combination of acyclovir and prednisolone over prednisolone alone.

The lack of benefit from antiviral therapy that is reported by Sullivan et al. conflicts with the results of a recent prospective, randomized, placebo-controlled study by Hato et al.[14] that compared a combination of valacyclovir (at a dose of 500 mg twice daily for 5 days) and prednisolone with placebo and prednisolone.[14] A complete recovery was seen in 96.5% of 114 patients who received valacyclovir and prednisolone, as compared with 89.7% of 107 patients who received placebo and prednisolone (an absolute risk reduction of 6.8%). More striking was the report of the full recovery of 90.1% of patients with complete facial palsy who were treated with valacyclovir and prednisolone, as compared with 75.0% of those treated with placebo and prednisolone. This finding extrapolates to a need to treat approximately 15 patients among the total group with Bell's palsy or approximately 7 patients in the subgroup with complete facial palsy to achieve one additional full recovery. The patients in the study by Hato et al. appear to have had more severe facial palsy than those in the study by Sullivan et al. (The average Yanagihara score in the study by Hato et al. was approximately 15, which falls between House–Brackmann grades 4 and 5, as compared with a mean score of 3.6 in the study by Sullivan et al.). In the study by Hato et al., the benefit of valacyclovir and prednisolone over placebo and prednisolone appeared to correlate with the severity of the facial palsy (an absolute risk reduction of 15.1% in patients with complete palsy and 5.7% in those with severe palsy, as compared with no reduction in those with moderate palsy). However, there were several methodologic limitations in the study by Hato et al. First, the investigators who were administering the treatment and assessing the outcome were aware of study-group assignments. Second, only 75% of patients who were enrolled in the study and underwent randomization were ultimately analyzed, as compared with 91 to 95% in their similar groups in the study by Sullivan et al.

How are the results from these two studies to be integrated into clinical practice? Although most patients with Bell's palsy improve spontaneously, the use of prednisolone within 72 hours after the onset of symptoms decreases permanent facial disfigurement. In the United States, oral prednisone (at a dose of 1 mg per kilogram of body weight for 7 to 10 days) is used more often than prednisolone, and the cost of prednisone is less than $11 for a course of 7 to 10 days. Furthermore, the number needed to treat (approximately nine) to see one additional complete recovery from facial palsy is small.

The study by Sullivan et al. clearly indicates that the addition of acyclovir provides no additional benefit to treatment with glucocorticoids alone. But what about valacyclovir? Valacyclovir is a prodrug that is nearly completely converted to acyclovir and L-valine and has substantially increased bioavailability, as compared with acyclovir. Both Hato et al. and Sullivan et al. show no benefit of antiviral therapy in patients with moderate palsy and thus provide no rationale for treating these patients with valacyclovir. The cost of a 5-day course of 500 mg of valacyclovir twice daily is approximately $70, and the number needed to treat for one additional full recovery in patients with complete facial palsy is approximately seven. Although the study by Hato et al. was methodologi-

cally flawed, the use of valacyclovir in combination with glucocorticoids could still be considered in patients with severe or complete facial palsy.

No potential conflict of interest relevant to this article was reported.

From the Departments of Neurology (D.H.G., K.L.T.), Microbiology (D.H.G., K.L.T.), and Medicine (K.L.T.), University of Colorado School of Medicine; and the Neurology Service, Denver Veterans Affairs Medical Center (K.L.T.) — both in Denver.

1. Mutsch M, Zhou W, Rhodes P, et al. Use of the inactivated intranasal influenza vaccine and the risk of Bell's palsy in Switzerland. N Engl J Med 2004;350:896-903.
2. Katusic SK, Beard CM, Wiederholt WC, Bergstralh EJ, Kurland LT. Incidence, clinical features, and prognosis in Bell's palsy, Rochester, Minnesota 1968-1982. Ann Neurol 1986;20:622-7.
3. Peitersen E. Bell's palsy: the spontaneous course of 2,500 peripheral facial nerve palsies of different etiologies. Acta Otolaryngol Suppl 2002;549:4-30.
4. *Idem*. The natural history of Bell's palsy. Am J Otol 1982;4:107-11.
5. Cawthorne T. The pathology and surgical treatment of Bell's palsy. Proc R Soc Med 1951;44:565-72.
6. Fowler EP Jr. Medical and surgical treatment of Bell's palsy. Laryngoscope 1958;68:1655-62.
7. Yetiser S, Kazkayas M, Altinok D, Karadeniz Y. Magnetic resonance imaging of the intratemporal facial nerve in idiopathic peripheral facial palsy. Clin Imaging 2003;27:77-81.
8. Murakami S, Mizobuchi M, Nakashiro Y, Doi T, Hato N, Yanagihara N. Bell palsy and herpes simplex virus: identification of viral DNA in endoneurial fluid and muscle. Ann Intern Med 1996;124:27-30.
9. Gilden DH. Bell's palsy. N Engl J Med 2004;351:1323-31.
10. De Diego JI, Prim MP, De Sarriá MJ, Madero R, Gavilán J. Idiopathic facial paralysis: a randomized, prospective, and controlled study using single-dose prednisone versus acyclovir three times daily. Laryngoscope 1998;108:573-5.
11. Sullivan FM, Swan IRC, Donnan PT, et al. Early treatment with prednisolone or acyclovir in Bell's palsy. N Engl J Med 2007;357:1598-607.
12. Grogan PM, Gronseth GS. Steroids, acyclovir, and surgery for Bell's palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:830-6.
13. Rowlands S, Hooper R, Hughes R, Burney P. The epidemiology and treatment of Bell's palsy in the UK. Eur J Neurol 2002;9:63-7.
14. Hato N, Yamada H, Kohno H, et al. Valacyclovir and prednisolone treatment for Bell's palsy: a multicenter, randomized, placebo-controlled study. Otol Neurotol 2007;28:408-13.

STAT3 Signaling and the Hyper-IgE Syndrome

David E. Levy, Ph.D., and Cynthia A. Loomis, M.D., Ph.D.

The Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signaling pathway has emerged over the past decade as a major relay between cell-surface receptors and cytokine responses. The human genome encodes four JAK family members — JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2) — and seven STAT proteins.[1] JAKs are protein tyrosine kinases that interact with the intracellular domains of cytokine receptors (Fig. 1) and that have enhanced catalytic activity toward substrate proteins after receptor activation. The primary JAK substrates are STAT proteins — latent transcription factors that require their tyrosine residues, and sometimes serine residues, to be phosphorylated before they can induce the transcription of target genes.

The primary model of JAK-STAT signaling was established by delineation of the interferon pathway — wherein the JAK-STAT signal-transduction system was discovered.[2] Oligomerization of cytokine receptors in response to ligand binding leads to transphosphorylation of associated JAK enzymes, stimulating their ability to phosphorylate both the cytoplasmic domains of the cytokine receptors and the subsequently recruited STAT proteins (Fig. 1). Once phosphorylated, the STAT proteins dimerize through interactions between the phosphotyrosine and SRC homology 2 (SH2) domains. Active dimers accumulate in the cell nucleus, bind specific DNA target sequences of gene promoters, and recruit coactivator and transcriptional regulatory proteins that drive gene expression. The requirement of signal-dependent phosphorylation of STAT tyrosine residues, coupled with the sensitivity of STAT to dephosphorylation by nuclear phosphatases, renders the protein a dynamic, sensitive on–off switch for gene expression.

Molecular genetic analysis of cells from humans and from engineered mice has revealed that STAT proteins usually have highly specific functions, dictated both by the specific receptors that serve as activators and by the intrinsic DNA binding preferences of STATs and thus their spectrum of target genes. This inherent specificity is most easily observed in the phenotypes of mice lacking individual *Stat* genes (Table 1). Mice lacking Stat1, a protein activated primarily by interfer-