To the Editor: A mild, ongoing inflammatory process may be involved in the pathophysiology of a subgroup of schizophrenia. Meta-analyses found add-on anti-inflammatory treatment to be effective in at least early stages of schizophrenia. Immunologically, a blunted type 1 (acute) immune response and shift to the type 2 (chronic) response have been described in schizophrenia before. Serum levels of the proinflammatory type 1 cytokine interferon gamma (IFN-γ) and in vitro IFN-γ production after stimulation were lower in samples from unmedicated schizophrenia patients than in those from healthy controls, although the findings are in part controversial. Therefore, the type 1 response stimulant IFN-γ was hypothesized to have a therapeutic effect. We describe the effects of adjunctive IFN-γ in 2 treatment-resistant schizophrenia inpatients.

Case reports. Mr A, a 47-year-old man with a 26-year history of DSM-IV-defined paranoid schizophrenia, was admitted to the hospital in 2012 because of an exacerbation of paranoid-hallucinatory symptoms. Inpatient antipsychotic treatment for 31 weeks with a combination of clozapine 500 mg/d (mean plasma level = 758 ng/mL), amisulpride 600 mg/d (mean plasma level = 670 ng/mL), and haloperidol 2.5 mg/d had no effect, and a series of 20 electroconvulsive therapy (ECT) treatments yielded only marginal effect.
Mr B, a 36-year-old man with a 13-year history of paranoid schizophrenia (DSM-IV), was admitted to the hospital in 2012 because of an exacerbation of auditory hallucinations and paranoid thinking. Inpatient antipsychotic treatment for 20 weeks with clozapine 700 mg/d (mean plasma level = 655 ng/mL), benperidol 25 mg/d (mean plasma level = 11.8 ng/mL), and prothipendyl 80 mg/d had no effect, and 25 ECT treatments improved symptoms only briefly.

Treatment with IFN-γ-1b was started in these patients, and their antipsychotic combinations were kept nearly constant during IFN-γ-1b therapy. Three injections of 0.5 mL recombinant human IFN-γ-1b were administered subcutaneously every week for 4 weeks to both patients as adjunctive treatment. The IFN-γ-1b dose was then tapered down over 2 and 3 weeks in Mr A and Mr B, respectively.

Psychopathology was assessed weekly with the Positive and Negative Syndrome Scale (PANSS). Both patients showed a marked clinical improvement: Mr A’s PANSS total score decreased from 119 to 93 after 7 weeks, and Mr B’s decreased from 132 to 96 after 6 weeks (Figure 1). The patients were carefully monitored for side effects, since short-term side effects such as fever, headache, muscle pains, or malaise are often found. In Mr A, a transient increase to double normal liver enzyme values was observed after 2 weeks; values returned to normal in the fourth week. No fever, fatigue, decreased drive, or appetite occurred.

Despite the availability of numerous antipsychotics, the long-term course of schizophrenia is more or less the same as in the pre-neuroleptic era, and new therapeutic approaches are needed. Immune-based therapies—successfully introduced in psychiatry by the Nobel laureate Julius Wagner von Jauregg—and later forgotten—are a promising new field. Stimulating the blunted part of the immune response with anti-inflammatory medication might be 2 sides of the same coin. For ethical reasons, immune-based therapies currently can be evaluated only as add-on therapies in psychiatry, mostly in treatment-resistant patients. A further limitation is the uncontrolled open-label treatment of these patients. Despite these limitations, the effects are promising, and studies of immune-based approaches are urgently required.

### References

2. Nitta M, Kishimoto T, Müller N, et al. Adjunctive use of nonsteroidal anti-

### Abbreviation: PANSS = Positive and Negative Syndrome Scale.