Blocking IL-1β to slow down progression of ALS?

Jos W. M. van der Meer[1] and Anna Simon

Department of General Internal Medicine, Radboud University Nijmegen Medical Centre, Geert Grooteplein 8, 6525 GA, Nijmegen, The Netherlands

ALS—in the United States more familiarly known as Lou Gehrig's disease—is a progressive motor neuron disease that is invariably fatal within years. Although it is the most common adult motor neuron disease, with a prevalence of 2 per 100,000 individuals, the pathogenesis of ALS has not been unraveled thus far, and there is no cure (1). The PNAS paper by Meissner et al. (2) focuses on mutant superoxide dismutase 1 (SOD1) and links this to the proinflammatory cytokine interleukin 1β (IL-1β). The number of specific therapies that block IL-1β signaling is growing, so how optimistic should we be for a therapy for ALS?

ALS is characterized by degeneration of motor neurons in the primary motor cortex, corticospinal tracts, brainstem, and spinal cord, leading to progressive muscular paralysis. Most cases of ALS are sporadic, but 5–10% of cases are familial, and the clinical phenotype of these forms is very similar. There is a significant body of research into the pathogenesis of ALS (1), a large part of which focuses on mutations in SOD1. Such mutated enzymes are found in 20% of patients with the familial form of ALS, and can also be detected in some patients with sporadic ALS (1). Transgenic mice expressing mutant SOD1 develop progressive loss of motor neurons and early death, in a disease that resembles human ALS. SOD1 is a cytoplasmic enzyme, ubiquitously expressed, which catalyzes the conversion of superoxide anions to hydrogen peroxide; therefore, oxidative damage was a likely first hypothesis for the mechanism of disease. This hypothesis was invalidated, however, when it was found that the effect of mutated SOD1 on ALS development was not related to enzyme activity. There are several other current hypotheses on the pathogenic effect of mutated SOD1 in ALS (1), and, most likely, the cause of disease will turn out to be multifactorial.

CNS Disease and Inflammation

At the same time, there is an increasing interest in the role of inflammation in the pathogenesis of CNS diseases of various origin (1, 3, 4), which parallels the increasing insight into the intricacies of innate immunity. One of the most potent mediators of inflammation is IL-1β (5). Because of its potency, expression of and signaling by IL-1β is tightly regulated on several levels. An important regulatory step is cleavage of a pro-IL-1β form to the active IL-1β by an enzyme called caspase-1, which was formerly known as IL-1β–converting enzyme (ICE). IL-1β has been intensely studied, not least because of its central role in a group of hereditary disorders characterized by fever and increased inflammation (6). This has even resulted in the recognition of a new category of disease: autoinflammatory diseases. In autoinflammation, which is distinct from autoimmunity, the defect is located in innate immunity, not in adaptive immunity. Of course this is more a spectrum than a black-and-white distinction, but the concept of autoinflammation has brought new insights in immunology and disease (6). Blocking IL-1β action has proven to be highly successful in the treatment of several autoinflammatory syndromes (6).

Elevated concentrations of IL-1β were detected in cerebrospinal fluid and spinal cord of ALS patients.

Traditionally, inflammation in the CNS in neurological disease was thought to be a secondary event, arising in response to neuron damage (3). Increasingly, however, there are indications that in some diseases, inflammation may be more central to the disease mechanism. This is also true for ALS (1, 3).

Interleukin-1 and ALS

There have been previous indications for a role of IL-1β in ALS. Elevated concentrations of IL-1β were detected in cerebrospinal fluid and spinal cord of ALS patients, and also in SOD1 mutant mice (3). When SOD1 mutant mice were crossed with mice that selectively express an inhibitor of caspase-1 in their neurons —thus blocking expression of mature IL-1β in neurons (but not in microglia or astrocytes)—disease onset of ALS was unchanged, but the mice had a much longer survival (27 vs. 12 d from disease onset until death) (7).

Meissner et al. (2) show that purified mutant SOD1 can directly stimulate microglia to activate caspase-1 and increase secretion of mature IL-1β, after cytoplasmic accumulation. They reproduced the findings of Friedlander et al. (7) that SOD1 transgenic mice crossed with mice that are caspase-1 deficient (completely, not selectively in the neurons) had similar disease onset but longer survival. They also crossed SOD1 transgenic mice with IL-1β–deficient mice, with similar results, proving that the caspase-1-inhibiting effect works through decreased IL-1β production (2). The fact that mice lacking IL-1β still develop ALS-like motor neuron degeneration, albeit with slower disease progression, suggests that inflammation is not the initiating factor in disease, but the longer survival does make this an avenue of interest for potential treatment to halt progression and increase survival in humans.

Meissner et al. (2) tried this in the concluding part of their study and were successful: treatment with the IL-1 blocker anakinra resulted in a similar prolonged survival and slowed disease progression, as seen in IL-1β–deficient mice (2). Meissner et al. started this treatment before the mice showed any sign of disease (which would be practically impossible to achieve in humans), but because the mice showed no change in time of onset of disease, the effect of IL-1 blockade is most likely more important during active disease than before disease onset.

Another factor to keep in mind is the high dose of anakinra used: 75–150 mg/kg, whereas in humans a dose of 1–2 mg/kg is usual. Anakinra is the IL-1β blocking agent that has been around for the longest time. It is a recombinant form of IL-1 receptor antagonist (IL-1ra), an endogenous competitive inhibitor of IL-1β signaling through the IL-1 receptor, and is a potent anti-inflammatory drug. However, it is a large protein (17 kDa), and has very low permeation into the cerebrospinal fluid [from <1% in healthy brains (8) to 2–4% in patients with subarachnoid hemorrhage (9)], besides having a very short half-life. Nevertheless, this low penetration into the cerebrospinal fluid does result in decrease of CNS inflammation in, for example, neonatal onset multisystem inflammatory

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[1]To whom correspondence should be addressed. E-mail: j.vandermeer@aig.umcn.nl.

disease (NOMID) (10). In addition, it should be borne in mind that in clinical trials in sepsis, anakinra was infused in dosages of 2 $mg \cdot kg^{-1} \cdot h^{-1}$ for 72 h, so higher dosages are feasible and safe (11). Newer inhibitors of IL-1 that were recently licensed for use in humans include canakinumab, a fully humanized monoclonal antibody to IL-1β, and rilonacept, a long-acting IL-1 receptor fusion protein; these are both active for a much longer time than anakinra. We have not found details on the CNS penetration of canakinumab or rilonacept.

Need for a Therapeutic Trial

So what can be expected from IL-1 blockade in ALS in humans? It is not likely to be a miracle intervention. By coincidence, we have recently had experience with anakinra in a patient with ALS (12). We treated a 62-y-old woman who had severe idiopathic cold urticaria for years with anakinra, with an excellent response with regard to the cold-induced inflammation. However, in the year before she presented to us, she had gradually developed neurological symptoms indicative of bulbar-onset ALS. After 3 wk of anakinra treatment, the patient reported subjectively improved swallowing and speech facility, but speech analysis did not reveal an objective improvement, and over the ensuing months, the neurological signs steadily progressed despite continued treatment with s.c. anakinra (100 mg daily). When her ALS had progressed significantly, we decided to try a series of i.v. anakinra 300-mg infusions (5 mg/kg) in an attempt to slow progression of neuron degeneration, but when this did not result in any neurological improvement after 10 injections, the patient was reverted to daily 100-mg anakinra s.c. for treatment of her urticaria. She died about 3 y after onset of clinical symptoms of ALS (12).

In the mice in the present study, an anakinra dose at least 20× higher than our highest dose was used to gain some effect on slowing disease progression. Any trial of IL-1 inhibition in human ALS should be performed in a placebo-controlled setting to detect any improvement in disease course and should probably be performed with high-dose inhibition to achieve adequate IL-1 inhibition in the CNS. An advantage of IL-1 inhibition is the absence of serious side effects, which might make such a trial practicable.

1. Rothstein JD (2009) Current hypotheses for the underlying biology of amyotrophic lateral sclerosis. *Ann Neurol* 65 (Suppl 1):S3–S9.
2. Meissner F, Molawi K, Zychlinsky A (2010) Mutant SOD1 induced IL-1β accelerates ALS pathogenesis. *Proc Natl Acad Sci USA* 107:13046–13050.
3. Papadimitriou D, et al. (2010) Inflammation in ALS and SMA: Sorting out the good from the evil. *Neurobiol Dis* 37:493–502.
4. Bartfai T, et al. (2007) Interleukin-1 system in CNS stress: Seizures, fever, and neurotrauma. *Ann N Y Acad Sci* 1113:173–177.
5. Dinarello CA (2009) Immunological and inflammatory functions of the interleukin-1 family. *Annu Rev Immunol* 27:519–550.
6. Masters SL, Simon A, Aksentijevich I, Kastner DL (2009) Horror autoinflammaticus: The molecular pathophysiology of autoinflammatory disease (*). *Annu Rev Immunol* 27:621–668.
7. Friedlander RM, Brown RH, Gagliardini V, Wang J, Yuan J (1997) Inhibition of ICE slows ALS in mice. *Nature* 388:31.
8. Fox E, et al. (2010) The serum and cerebrospinal fluid pharmacokinetics of anakinra after intravenous administration to non-human primates. *J Neuroimmunol* 223:138–140.
9. Gueorguieva I, et al. (2008) Pharmacokinetic modelling of interleukin-1 receptor antagonist in plasma and cerebrospinal fluid of patients following subarachnoid haemorrhage. *Br J Clin Pharmacol* 65:317–325.
10. Goldbach-Mansky R, et al. (2006) Neonatal-onset multisystem inflammatory disease responsive to interleukin-1beta inhibition. *N Engl J Med* 355:581–592.
11. Opal SM, et al. (1997) Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: A phase III, randomized, double-blind, placebo-controlled, multicenter trial. The Interleukin-1 Receptor Antagonist Sepsis Investigator Group. *Crit Care Med* 25:1115–1124.
12. Bodar EJ, Simon A, de Visser M, van der Meer JWM (2009) Complete remission of severe idiopathic cold urticaria on interleukin-1 receptor antagonist (anakinra). *Neth J Med* 67:302–305.