Reverse-Transcriptase Inhibitors in the Aicardi–Goutières Syndrome


To cite this version:

HAL Id: pasteur-01974160
https://hal-pasteur.archives-ouvertes.fr/pasteur-01974160
Submitted on 8 Jan 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
Reverse-Transcriptase Inhibitors in the Aicardi–Goutières Syndrome

TO THE EDITOR: The Aicardi–Goutières syndrome is a genetic encephalopathy that is associated with childhood illness and death. The syndrome is hypothesized to be due to misidentification of self-derived nucleic acids as nonself and the subsequent induction of a type I interferon–mediated response that simulates an antiviral reaction. Endogenous retroelements, mobile genetic elements that can be transcribed to RNA and then to DNA by reverse transcription, constitute 40% of the human genome and represent a potential source of immunostimulatory nucleic acid in patients with this syndrome.

In a single-center, open-label, pilot study involving patients with the Aicardi–Goutières syndrome (ClinicalTrials.gov number, NCT02363452), we administered a combination of three nucleoside analogue reverse-transcriptase inhibitors — abacavir, lamivudine, and zidovudine — for 12 months, at doses used in children with human immunodeficiency virus type 1 (HIV-1) infection. The study protocol is available with the full text of this letter at NEJM.org. The primary aim was to determine the effect of treatment on interferon signaling, with the median interferon score across all 8 patients falling from 9.66 (interquartile range, 6.51 to 13.23) to 5.33 (interquartile range, 2.76 to 10.90) (P<0.001) (Fig. 1A). Interferon-α protein levels in serum and plasma and interferon antiviral activity in CSF were also reduced with treatment (Table S3 in the Supplementary Appendix). This effect was greatest among the 4 patients with mutations in components of the RNase H2 complex (with the median score in these 4 patients falling from 8.16 [interquartile range, 5.41 to 11.94] to 3.51 [interquartile range, 2.49 to 5.46]). RNA sequencing indicated a reduction of global interferon-stimulated gene expression after 12 months of treatment and a return...
to pretreatment levels 6 months after discontinuation of therapy (Figs. S5 and S6 in the Supplementary Appendix). There was an increase in cerebral blood flow during the treatment period in 3 of 5 patients with data that could be interpreted (Fig. S8 and Table S7 in the Supplementary Appendix).

These results support the hypothesis that HIV-1 reverse-transcriptase therapy can reduce interferon signaling in patients with the Aicardi–Goutières syndrome by inhibition of reverse transcription of endogenous retroelements. Changes in interferon signaling and cerebral blood flow suggest that treatment could have clinical value, perhaps in combination with other therapies (e.g., inhibitors of Janus kinase 1 and 2).4 The open-label design of the study and small sample require that a larger group of patients be evaluated in a controlled clinical trial.

Gillian I. Rice, Ph.D.
University of Manchester
Manchester, United Kingdom

Figure 1. Measures of Interferon Status in Eight Patients Completing 12 Months of Therapy.

Panel A shows the interferon score in blood, with higher scores indicating greater interferon signaling. There were 18 recorded values before the screening period, 30 recorded values during the screening period (6 months up to and including day 0), 40 recorded values during the 12-month treatment period, and 8 recorded values at month 18 (6 months after the discontinuation of treatment). Red lines represent the median values according to time period. The dashed line indicates the mean interferon score of controls plus 2 SD; values above this line (i.e., >2.47) are considered to be abnormal. Panel B shows a comparison of interferon scores in blood in the 6 months before treatment, during the treatment period, and after treatment (at month 18), performed with the use of a nonlinear mixed-effects model. Panel C shows the interferon-α protein level in blood, Panel D the interferon score in blood, Panel E the interferon-α protein level in cerebrospinal fluid (CSF), and Panel F interferon activity in CSF at the indicated time points. Two patients (Patient 5 and Patient 10) did not undergo lumbar puncture. In two other patients (Patient 3 and Patient 4), an insufficient CSF sample was available at day 0, month 12, or both for assessment of the interferon-α protein level, interferon activity, or both. The correlation coefficient between the interferon-α protein level in blood and the interferon score in blood was 0.704 (P<0.001).
Correspondence

Candice Meyzer, M.D.
Naïm Bouazza, Ph.D.
Assistance Publique–Hôpitaux de Paris
Paris, France

Marie Hully, M.D.
Nathalie Boddart, M.D.
Hôpital Necker–Enfants Malades
Paris, France

Michaela Semeraro, M.D., Ph.D.
Université Paris Descartes
Paris, France

Leo A.H. Zeef, Ph.D.
University of Manchester
Manchester, United Kingdom

Florence Renaldo, M.D.
Hôpital Robert Debré
Paris, France

Vincent Bondet, Ph.D.
Darragh Duffy, Ph.D.
Alba Llibre, Ph.D.
Institut Pasteur
Paris, France

Jinmi Baek, M.Sc.
Mame N. Sambe, B.Sc.
Elodie Henry, M.Sc.
Valerie Jolaine, M.Sc.
Assistance Publique–Hôpitaux de Paris
Paris, France

Christine Barnerias, M.D.
Hôpital Necker–Enfants Malades
Paris, France

Magalie Barth, M.D.
Centre Hospitalier Universitaire Angers
Angers, France

Alexandre Belot, M.D., Ph.D.
University of Lyon
Lyon, France

Claude Cances, M.D.
Centre Hospitalier Universitaire Toulouse
Toulouse, France

Francois-Guillaume Debray, M.D., Ph.D.
University of Liège
Liège, Belgium

Diane Doummar, M.D.
Hôpital Armand Trousseau
Paris, France

Marie-Louise Frémond, M.D.
Naoki Kitabayashi, B.Sc.
Alice Lepelley, Ph.D.
Institut Imagine
Paris, France

Virginie Levrat, M.D.
Centre Hospitalier Annecy Genevois
Pringy, France

Isabelle Melki, M.D., Ph.D.
Hôpital Robert Debré
Paris, France

Pierre Meyer, M.D.
Université de Montpellier
Montpellier, France

Marie-Christine Nougues, M.D.
Hôpital Armand Trousseau
Paris, France

Mathieu P. Rodero, Ph.D.
Institut Imagine
Paris, France

Diana Rodriguez, M.D., Ph.D.
Sorbonne Université
Paris, France

Agathe Roubertie, M.D., Ph.D.
Centre Hospitalier Universitaire de Montpellier
Montpellier, France

Luis Seabra, M.Sc.
Institut Imagine
Paris, France

Carolina Uggenti, Ph.D.
University of Edinburgh
Edinburgh, United Kingdom

Hendy Abdoul, M.D., Ph.D.
Jean-Marc Treluyer, M.D.
Assistance Publique–Hôpitaux de Paris
Paris, France

Isabelle Desguerre, M.D.
Stéphane Blanche, M.D.
Hôpital Necker–Enfants Malades
Paris, France

Yanick J. Crow, M.D., Ph.D.
University of Edinburgh
Edinburgh, United Kingdom
yanickcrow@mac.com

Supported by grants from the European Leukodystrophy Association (ELA 2012-0081), the European Research Council (GA 309449 and 786142-E-T1IFNs), ERA-NET Neuron (MR/M501803/1), and the French National Research Agency (ANR-10-IAHU-01 and CE17001002). Medications were provided by GlaxoSmithKline and Viiv Healthcare.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.


DOI: 10.1056/NEJMc1810983