HIV-1 suppression by early treatment with hydroxyurea, didanosine, and a protease inhibitor

Julianna Lisziewicz, Heiko Jessen, Diana Finzi, Robert F Siliciano, Franco Lori

Most HIV-1 production occurs in dividing (activated) T-lymphocytes. Non-dividing resting lymphocytes and macrophages, however, might be long-term reservoirs for HIV-1. We wanted to increase the antiviral efficacy of combination therapies by targeting simultaneously reservoir cells and the virus. Hydroxyurea blocks cellular activation necessary for viral replication in CD4 T-lymphocytes, protease-inhibitors inhibit HIV-1 replication in dividing cells, and hydroxyurea with didanosine is effective in non-dividing cells.1,2

Eleven individuals were treated within 2 months after the onset of symptoms of primary HIV-1 infection and before complete serconversion, with a combination of hydroxyurea, didanosine, and indinavir. No greater than grade 2 toxicity was found, except for grade 3 episodes of nephrolithiasis in two patients; toxic events were resolved by switching from indinavir to nelfinavir. CD4 counts increased significantly by an average of 207 whereas CD8 counts decreased by an average of 399. CD4/CD8 ratio returned to normal in nine of eleven treated patients. This increase of CD4 counts was unexpected because the combination of hydroxyurea and didanosine, despite synergistic HIV-1 inhibition, in symptom-free individuals resulted in a significant increase of CD4 T-lymphocytes.1

Plasma viraemia, starting from an average of 509 233 copies/mL, became undetectable in all patients within 8 weeks of treatment, and remained undetectable throughout the observed course of treatment for up to 17 months (<50 copies/mL). It is likely that such an early, significant, and long-lasting reduction in viral load will improve the prognosis of these patients. In six of six patients no HIV-1 RNA was detectable (400 copies/mL) in semen. No HIV-1 RNA was found despite an extensive and repeated analysis (44 million cells screened) in lymph nodes of two of three individuals; in a third, HIV-1 RNA was found in three of 44 million cells. However, after this patient stopped taking antiretroviral medications, there was no viral rebound, and CD4 counts and CD4/CD8 ratio remained normal for over 1 year. HIV-1 DNA was undetectable by nested PCR analysis in this patient’s lymph node 78 days after stopping treatment and replication-competent virus was recoverable with unprecedented low frequency from resting CD4 T-lymphocytes (<1 cell/10 million harbouring latent HIV-1) 1 year after stopping treatment.

These results show that treatment of acutely-infected individuals with potent antiviral drugs having different mechanisms of action and affecting multiple compartments results in a profound effect on the natural evolution of primary HIV-1 infection. Absence of HIV-1 rebound after stopping treatment has so far been described only in patients treated with the combination containing hydroxyurea and didanosine.3 Combining drugs targeting both the cell and the virus in multiple compartments might be critical to achieve maximal and sustained inhibition of HIV-1.

We thank M Stevens and Bristol-Myers Squibb for financial support, C Fox for the in-situ analysis, members of Right’s laboratory, especially A DeAntoni, A Foli, A Malýkh, L Barker, and H Jessen’s Praxis team, R Shroeder and M Heinrich.1 Lori F, Malýkh A, Cara A, et al. Hydroxyurea as an inhibitor of human immunodeficiency virus-type 1 replication. Science. 1994; 266: 801–05.

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Q1 & Q3=Quartiles 1 and 3.

Patients 3 and 4 stopped treatment after 6 and 3 months; values here refer to the period of treatment.

Patients 10 and 11 also received delavirdine 400 mg three times a day.

Primary HIV-1 infection treated with hydroxyurea, didanosine, and indinavir
Cortical processing in persistent vegetative state

D K Menon, A M Owen, E J Williams, P S Minhas, C M C Allen, S J Boniface, J D Pickard, and the Wolfson Brain Imaging Centre Team*

Reductions in cerebral blood flow and glucose metabolism have been reported in patients in persistent vegetative state. A few studies have suggested residual cortical activity. Objective assessment of residual cognitive function is difficult because motor responses may be small or inconsistent. We used positron emission tomography to study covert cognitive processing in a patient in a persistent vegetative state.

A 26-year-old woman had an acute febrile illness and became comatose. Clinical findings and examination of cerebrospinal fluid were consistent with acute disseminated encephalomyelitis. Magnetic resonance imaging showed hyperintensity in the brainstem, and small foci of hyperintensity in both thalami and in the medial right temporal lobe on T2-weighted images. 4 months after admission, she had a tracheostomy, was fed through a gastrotomy, and was doubly incontinent. Her eyes opened spontaneously and she had sleep-wake cycles. Despite repeated examination, she showed no consistent spontaneous or elicited motor responses or eye movements to suggest she could communicate. Electroencephalograms were consistent with a thalamic lesion, complicated by possible cortical ischaemia. The pons and mid-brain components of the brainstem auditory evoked responses were abnormal on both sides, but a delayed auditory oddball P300 could be detected. Functional imaging studies were undertaken to look for evidence of preserved but covert cortical processing.

Face-recognition was tested after a rapid infusion of H215O. Photographs of faces familiar to the patient were shown on a computer screen. Control images were generated by repixellating the same photographs to remove structure from the images. Subtraction of control from test images showed a significant focus of activation in the right fusiform gyrus (Brodmann’s area 37), which spread ventrally to the most dorsal part of the cerebellum and posteriorly to include extrastriate areas 18 and 19 (figure). 2 months after this study (6 months after her illness began) she became increasingly responsive, and at the time of acceptance of this manuscript (8 months after her illness) she clearly recognised faces and used short sentences, such as “Don’t like physiotherapy.”

Activation patterns in this patient correlate closely with results from previous studies with similar tests. It is difficult to make judgments about awareness or consciousness based on these results; however, it is clear that she not only perceived visual stimuli, but also processed them to some extent. Further studies may more closely correlate functional imaging with behavioural assessment, electrophysiological findings, and eventual outcome.


Non-steroidal anti-inflammatory drugs and metformin: a cause for concern?

N N Chan, N J Faue1, M D Feher

Patients with type 2 diabetes who are treated with metformin are at risk of metformin-associated lactic acidosis if they develop renal failure.1 Impairment of renal function in diabetes may be a consequence of diabetic nephropathy, or secondary to metabolic, immunological, or drug factors. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed and are known to cause renal failure. We describe a case of severe lactic acidosis in a patient with type 2 diabetes mellitus on long-term metformin therapy, who developed acute renal failure after recent treatment with a NSAID.

A 57-year-old Asian woman with type 2 diabetes mellitus who had been treated with metformin (500 mg twice daily) for 15 years was admitted with general malaise, abdominal pain, nausea, and vomiting. 2 months before admission indomethacin (50 mg four times daily) was prescribed for severe backache. There was no history of analgesic abuse or previous renal disease. On admission, she was clinically euvoaemic but oliguric with a blood pressure (BP) of 180/90 mm Hg. There was no evidence of loin tenderness. Fundoscopy showed no signs of diabetic retinopathy. Initial biochemical findings confirmed acute renal failure and severe metabolic acidosis with sodium 131 mmol/L, potassium 4.6 mmol/L, urea 28 mmol/L, creatinine 480 μmol/L, pH 6.82, standard bicarbonate 1.2 mmol/L, glucose 13.6 mmol/L, and corrected calcium 2.1 mmol/L. Lactate was greatly raised at 21.1 mmol/L (normal range 0.1–1.2 mmol/L). Plasma alcohol was not detected. No immunological cause of glomerulonephritis was identified. Urinalysis showed no ketones or protein. Electrocardiogram revealed no evidence of acute myocardial ischaemia. Normal size kidneys without obstruction were confirmed by ultrasound scan. Subsequent management in the intensive care unit included intravenous fluids, and inotrope and insulin infusion. Both metformin and indomethacin were discontinued. Her condition gradually improved and she was discharged with stable impaired renal function (urea 17 mmol/L and creatinine 220 μmol/L), BP 100/70 mm Hg, and diabetes requiring only dietary control.

Although diabetic nephropathy is a potential cause of renal failure in all diabetic patients, the absence of diabetic retinopathy and proteinuria would suggest a non-diabetic cause in this case. The cause of the acute renal failure in this patient was most likely due to the NSAID which is known to reduce glomerular filtration rate with subsequent impairment of renal function.1 Metformin is excreted by the kidneys2 and may accumulate in the presence of acute renal insufficiency, contributing to the development of lactic acidosis.

It is highly likely that considerable numbers of patients with diabetes have received this drug combination. However, to date there have been only three cases of metformin-associated lactic acidosis with concurrent NSAID therapy (two of whom had renal failure) reported to the Committee on Safety of Medicines in the UK. The manufacturers’ data sheets for both drugs do not have a warning of potential hazard for this combination. Drugs which may precipitate renal failure, including NSAIDs, should be used with caution in type 2 diabetic patients treated with metformin.

2. Safadi R, Dranitski-Ilhalel M, Popovtzer M, Ben-Yehuda A.

Short-term haemodynamic effects of BQ-123, a selective endothelin ET1 receptor antagonist, in chronic heart failure

Peter J Cowburn, John G F Cleland, John D McArthur, Margaret R MacLean, John V McMurray, Henry J Dargie

Plasma concentrations of endothelin-1 (ET1), a potent vasoconstrictor peptide, are raised in patients with chronic heart failure, correlate with the symptomatic and haemodynamic severity of heart failure, and predict prognosis. The vasoconstrictor action of ET1 is mediated through two high-affinity endothelin receptor subtypes on smooth muscle, denoted ET1 and ET2. ET1 receptors are also present on the vascular endothelium where they mediate vasodilatation via nitric oxide and/or prostaglandins. ET2 receptors may also have a role in the clearance of ET1. Functional significance of ET1 receptors in chronic heart failure is not clear, leading to debate as to whether a selective ET1 receptor antagonist or a non-selective ET1/ET2 receptor antagonist might be the better therapeutic agent in chronic heart failure.

Bosentan, a non-selective ET1/ET2-receptor antagonist, has led to improved pulmonary and systemic haemodynamic indices in patients with chronic heart failure in whom ACE inhibitors had been withheld. Animal models of heart failure show that chronic administration of selective ET1 antagonists has beneficial effects on left ventricular and myocyte function, and improves prognosis. We investigated the haemodynamic effects of BQ-123, an ET1 selective antagonist in patients with chronic heart failure secondary to left ventricular systolic dysfunction.

Ten patients with stable chronic heart failure, taking diuretics and an ACE inhibitor (n=9) or an angiotensin-II receptor antagonist (1), took part in the study. In contrast with other reports, patients took their usual medications on the day of study. Haemodynamics were measured with a pulmonary thermodilution catheter and a femoral arterial line. After a 30 min saline infusion to establish baseline values, BQ-123 (Clinalfa, Switzerland) was infused at 200 nmol/min (100 nmol/min for first two patients) for 60 min through a central venous catheter. In eight patients, during the last 15 min of the infusion, ET1 was co-infused at a dose previously shown to cause systemic vasconstriction in patients with chronic heart failure (15 pmol/min).1

Infusion of BQ-123 led to systemic vasodilatation: mean arterial pressure (SEM) [5] to [79±4] mm Hg, p<0.01 and systemic vascular resistance ([14±8] to [130±7] dynes·s·cm−2, p<0.001) fell, whereas cardiac index rose ([2.39±0.15] to [2.51±0.13] L/min/m², p<0.05). Although mean pulmonary artery pressure fell ([22±3] to [19±3] mm Hg, 

THE LANCET • Vol 352 • July 18, 1998 201
Our study shows that a selective ETA antagonist has beneficial haemodynamic effects in patients receiving long-term ACE inhibitors. This study also suggests that care may be required when starting endothelin antagonists in patients with severe chronic heart failure, as is the case with ACE inhibitors. Whether selective ET_{A} or non-selective ET_{A}/ET_{B}-receptor antagonists are of greater therapeutic benefit for patients with chronic heart failure needs to be determined in long-term trials.

p=0.01), the fall in pulmonary vascular resistance did not reach statistical significance (178[24] to 153[13] dynes s^{-1} cm^{-5}, p=0.13). There was no change in heart rate (70[5] to 71[6]/min). ET_{1}, when co-infused with BQ-123, did not lead to systemic vasoconstriction.

One episode of syncope and bradycardia occurred after infusion of BQ-123 in a patient with markedly elevated pulmonary artery pressures (61/27 mm Hg, mean 40 mm Hg). There were no other side-effects.

Our study shows that a selective ET_{A} antagonist has beneficial haemodynamic effects in patients receiving long-term ACE inhibitors. This study also suggests that care may be required when starting endothelin antagonists in patients with severe chronic heart failure, as is the case with ACE inhibitors. Whether selective ET_{A}/ET_{B}-receptor antagonists are of greater therapeutic benefit for patients with chronic heart failure needs to be determined in long-term trials.

Severe cutaneous reaction due to terazosin

Natalia Hernández-Cano, Pedro Herranz, Teresa E Lázaro, Matías Mayor, Mariano Casado

A 56-year-old white man consulted us with a generalised rash that had occurred 3 days after being started on terazosin 2 mg/day for benign prostatic hyperplasia. His medical and family history was unremarkable, and he had not taken any other medication. He had mild fever and asthenia, and pruritus was intense. We saw a widespread eruption of scaling erythematous plaques with a violaceous hue on the trunk (figure) and extremities, affecting his palms and soles but sparing the mucous membranes. The lesions had sharp borders and covered almost the entire body surface, with patches of normal skin among them. We noted non-specific inguinal lymphadenopathy, but the remainder of clinical examination was normal. Haematological and biochemical parameters, including liver-function tests, were normal, except for mild leucocytosis (leucocytes 14·4 x 10^9/L) and a slightly raised erythrocyte sedimentation rate (25 mm/h). Serological tests for antinuclear antibodies, rheumatoid factor, syphilis, hepatitis B and C, and Epstein-Barr virus were all negative. Histopathological assessment of a skin biopsy sample showed a pattern suggestive of a drug reaction, consisting of subtle basal spongiosis and mild lymphocytic exocytosis, with some apoptotic keratinocytes in the basal epidermal layer. In addition, a mild perivascular lymphocytic infiltrate with scant eosinophils was present in the upper dermis. Terazosin was stopped, and treatment with oral methylprednisolone (40 mg/day) and emollients resulted in complete recovery in 2 weeks.

Terazosin is a long-acting a-1 selective blocking agent that was used originally for treatment of hypertension. Multicentre placebo-controlled studies have reported its efficacy in benign prostatic hypertrophy. The rare and usually mild adverse effects related to the drug’s pharmacological action are dose-related and include headache, dizziness, and asthenia. Adverse cutaneous reactions are rare, although non-specific mild rashes have been occasionally reported.

In view of the clear temporal relation between the onset of terazosin therapy and the cutaneous eruption and the resolution of the skin lesions when terazosin was used, we believe that a drug reaction was responsible for this case.

withdrawn, and the absence of any other attributable medication, we believe that the reaction presented in our patient can be clearly attributed to terazosin. We have found no previous reports of severe drug reactions due to this drug.

Widespread use of terazosin for the management of benign prostatic hyperplasia may lead to an increase in its side-effects. Therefore, internists, urologists, and cardiologists must bear in mind the possibility of cutaneous reactions.


### Department of Dermatology, La Paz University Hospital, Pº Castellana 261, 28046 Madrid, Spain (N Hernández-Cano)

#### Lymphocytapheresis to treat rapidly progressive glomerulonephritis: a randomised comparison with steroid-pulse treatment

Takashi Furuta, Osamu Hotta, Naoko Yusa, Ikuo Horigome, Shigemi Chiba, Yoshio Taguma

Rapidly progressive glomerulonephritis (RPGN) may progress to end-stage renal failure within weeks and to death from organ damage induced by systemic vasculitis or from immune system failure due to immunosuppressive therapy. Death or the need for dialysis has variously been reported to occur in 17% to 73% of patients treated for RPGN.1,2 The need exists for a means promptly to stop death from organ damage induced by systemic vasculitis or from immune system failure due to immunosuppressive therapy. Death or the need for dialysis has variously been reported to occur in 17% to 73% of patients treated for RPGN. The need exists for a means promptly to stop death from organ damage induced by systemic vasculitis or from immune system failure due to immunosuppressive therapy. Death or the need for dialysis has variously been reported to occur in 17% to 73% of patients treated for RPGN.

The freedom from post-treatment suppression of the CD4/8 ratio also suggests lymphocytapheresis is the safer procedure.


A tooth per child?
Kaare Christensen, David Gaist, Bernard Jeune, James W Vaupel

“A child, a tooth” is how a common proverb (in German [ein Kind, ein Zahn], Danish [et barn, en tand], Russian, and Japanese) quantifies the cost to mothers of childbearing. We used the Longitudinal Study of Ageing Danish Twins (LSADT) to test whether the number of children a woman has is related to the number of teeth she ends up losing.

The LSADT comprises twins aged 73 or older in the nationwide Danish Twin Registry. In 1995 and 1997, 2978 individuals—77% of the twins—were interviewed.1 Information on teeth, fertility, and social status was obtained for 97% of them. Twins and their spouses were assigned to one of five social classes,2 with responders being assigned to the social status of their spouse (alive or deceased) if it was known.3

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For women, regardless of social status, the number of teeth is negatively correlated with number of children (figure). For men, the correlation is negligible. Women of low social status lost about one additional tooth per child, whereas women of high social status lost about one additional tooth per two children: linear-regression estimates are 0·77 (p<0·001) and 0·42 (p<0·001) for the two social groups. Regardless of how many children they had, men and women of high status had about seven to nine more teeth on average than men and women of low status. Two smaller Swedish studies report findings that are similar but less clear.14

Our sample included 34 pairs of identical female twins who shared the same social status but who had different numbers of children and who fell into different dental categories. In 28 of these pairs, the twin with more children had fewer teeth (p<0·001). No such relationship was found for male twin pairs. In historic and prehistoric populations, caries and loss of teeth increased the risk of death.7 The long-term costs of childbearing on women’s health may have been substantial and they may still be significant.

This study was supported by a grant from the National Institute of Aging, US (P01-AG08761). The activities of the Danish Center for Demographic Research are supported by a grant from the Danish National Research Foundation.

4 Halling A, Bengtsson C. The number of children, use of oral contraceptives and menopausal status in relation to the number of remaining teeth and the periodontal bone height. Community Dent Health 1989; 6: 39–45.