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Poly-L-Lactic Acid for the Treatment of Facial Wasting

Lafaurie M, Dolivo M, Porcher R, Rudant J, Madelaine I, Molina J-M. *Treatment of facial lipoatrophy with intradermal injections of polylactic acid in HIV-infected patients****. J Acquir Immune Defic Syndr. April 1, 2005;38(4):393-398.***

Lipodystrophy syndromes are one of the most common complications of current HIV treatment and are a cause of much distress for many patients. Lipodystrophy can take many forms, including lipoaccumulation and lipoatrophy. Although we know that facial lipoatrophy is characterized by maxillary or temporal wasting, the exact etiology or mechanism has yet to be elucidated. But it is clear that the dramatic changes caused by facial lipoatrophy result in significant self esteem and quality of life issues for patients. Since it's a combination of HIV itself and perhaps certain antiretrovirals more than others that causes this problem, various treatments and interventions, such as switching treatments, have not had much success at reversing or preventing the problem. This has led providers and their patients to seek other solutions.

Possible cosmetic solutions have included plastic surgery and filling the atrophic area with inert, synthetic material to "bulk" up the affected area. Poly-L-lactic acid (PLA, New-Fill, Sculptra) is a synthetic injectable that was approved by the U.S. Food and Drug Administration (FDA) in August 2004 for the indication of facial lipoatrophy in people with HIV. A clinical trial by Matthieu Lafaurie et al sought to assess the safety and patient perceived efficacy of poly-L-lactic acid injections for the treatment of facial lipoatrophy.

The prospective, open-label, single-arm study was conducted at a medical center in France. Adult patients with obvious facial atrophy and a CD4+ cell count above 200 cells/mm^3 were included. Patients were screened during an initial visit. On subsequent visits a dermatologist performed several intradermal injections in each cheek. Ice and massage to the cheeks were then applied. Injections were performed every 2 weeks, for a minimum of at least 3 sets of injections. Safety was assessed at each visit. The primary endpoint was self-perception of improvement using a visual analog scale from 1-10. Quality of life SF-36 questionnaires, digital photographs and three-

dimensional digital photographs were also performed before and after the injections. Patients were followed for up to 12 months.

Ninety-eight patients were screened and 94 patients received at least one injection. Of these, 94% were men, with a median age of 44 years. All but 4 of the participants were on highly active antiretroviral therapy (HAART), with a median CD4+ cell count of 500 cells/mm^3. The median number of injections per cheek per patient was 5. Over 75% of the patients reported mild pain at the injection sites. No infectious complications were seen. In 12 cases, 2-4 mm subcutaneous noninflammatory nodules were seen. One patient experienced an anaphylactic reaction 2 days after the first injection, which resolved without further incident. The visual analog scale improved from 3.4/10 to 6.8/10 at the end of treatment. Eighty-two percent of the patients perceived some improvement by the end of treatment. Quality of life scores did not change after treatment. By digital photography, the median increase in dermal thickness was 1.9 mm, increasing to 2.3 mm by the last follow-up visit.

Interestingly, 2 blinded observers were asked to assess and distinguish baseline and follow-up photographs. The observers were only able to correctly determine the correct photographic sequence for about 65% of the patients and there was very little agreement between observers. Seventeen patients underwent additional injections after the initial period.

This study concluded that poly-L-lactic acid injections were safe, reasonably well tolerated and resulted in a self-perceived improvement in lipoatrophy, which persisted up to 15 months after the last injection. However, the quality of life instrument used did not register any significant improvement in quality of life. Further studies of poly-L-lactic acid will be needed to determine the optimal injection frequency and amount needed for administration.

On a practical note, this treatment is not covered by most private or public health insurance in the United States and, depending on the number of injections needed, treatment can cost up to $6,000. Since the benefits of this treatment do not last longer than 24 months, this can be an extremely expensive procedure to get and maintain.

The Impact of Patient Knowledge on HAART Initiation

Gellaitry G, Cooper V, Davis C, Fisher M, Leake Date H, Horne R. *Patients' perception of information about HAART: impact on treatment decisions****. AIDS Care. April 2005;17(3):367-376.***

One of the challenges of providing HIV care is to properly communicate to patients the reasons for starting treatment and then to prescribe HIV medications. This usually requires some fairly complicated explanations. Some providers even give short lessons just to make sure the often-complex issue of HIV treatment and why adherence is so critical are understood.

But how does one evaluate whether patients have been given, and internalized, sufficient information in order to make good treatment decisions? A study by Grace Gellaitry and colleagues from the United Kingdom sets out to answer this question. They looked at whether patients thought they had been given sufficient information about HIV treatment, toxicities and side effects and how that affected whether the patients chose to initiate HIV treatment.

Patients were given a questionnaire called the Satisfaction with Information about Medicine Scale (SIMS) to assess their perception about the quality of information they received regarding HAART. The questions included: "Were you told how to use your medicine?" and "Were you told what to do if you experience a side effect?" Patients then rated how much information they received.

Patients also completed the Specific Concerns scale of the Beliefs about Medicines Questionnaire (BMQ). Questions included concrete and abstract scenarios about medication side effects. Finally, patients were given the Patient Assessment of Sources of Medicines Information Questionnaire (PASMIQ) to determine what sources, such as family, doctors, Internet, etc., were helpful in making treatment decisions.

Of the 174 recruited patients, 115 completed the questionnaires. Over 90% were gay men, and the mean age was 38 years. About half had asymptomatic HIV infection. The median CD4+ cell count and viral load was 214 cells/mm^3 and 213,636 copies/mL, respectively. About two thirds were antiretroviral naive.

There was wide variation of SIMS scores. Only 42% were more than 80% satisfied with the

information they received. For essentially all items on the SIMS survey that pertained to information about action, usage or potential problems of HAART, patients who declined HIV treatment were less satisfied with the information they received than were those who accepted treatment. The patients who accepted treatment found HIV specialists (75%) or hospital pharmacists (70%) very helpful as sources of information. A little less than half found other HIV patients, the Internet or voluntary organizations as helpful or very helpful. Local pharmacists, general practitioners or patient groups were found not to be helpful.

Patients who declined HAART tended to have a higher BMQ score, which meant that they were more concerned about potential side effects than those who had accepted treatment were.

In a multivariate analysis that looked at various score and demographic parameters, stronger concerns and a longer HIV infection period correlated with a lower probability of starting HAART, whereas higher SIMS scores were associated with a greater likelihood of starting HAART.

This study highlights the fact that providers need to do a better job tailoring communication to patients and explaining the reasons for HIV treatment. More importantly, patients need to be provided with more details about both possible regimens and the potential for side effects.

The patients in this study were more likely to listen and accept information from their HIV provider than from other sources. The study is limited by the demographic group that was analyzed. It is unclear whether women or other risk groups would respond similarly. It is likely that educating other groups (i.e., lower educational or socio-demographic groups) would pose even greater challenges in effectively communicating treatment decisions by providers.

Antivirogram vs. PhenoSense Assays

Zhang J, Rhee S-Y, Taylor J, Shafer RW. *Comparison of the precision and sensitivity of the Antivirogram and PhenoSense HIV drug susceptibility assays****. J Acquir Immune Defic Syndr. April 1, 2005;38(4):439-444.***

Antiretroviral resistance testing has become part of standard of care and is recommended by the U.S. Department of Health and Human Services' HIV treatment guidelines for use in various clinical situations.

There are 2 types of resistance assays: genotypic and phenotypic. Genotyping produces a viral genetic sequence, after which interpretative software and rules-based algorithms determine the significance and impact of specific drug-associated mutations. There are two U.S. FDA-approved antiretroviral genotypic resistance assays available: Trugene (Bayer) and ViroSeq (Celera and Applied Biosystems). Other homebrew assays are utilized widely as well. Phenotypic assays on the other hand use a portion of the patient's virus (*RT* and *Pr* genes) inserted into an infectious virus that is then grown in cell culture in the presence of different concentrations of HIV drugs. The susceptibility or loss of susceptibility of a patient's virus to each antiretroviral drug is then determined.

There are currently 3 commercially available phenotypic resistance tests available: Phenoscript (VIRalliance), PhenoSense (ViroLogic) and Antivirogram (Virco) assays. Each proprietary technology performs the assay somewhat differently, but the results are usually expressed as the "fold change" or drug concentration that is required to inhibit the patient's virus compared to a wild-type lab strain without any drug mutations.

There have been relatively few published studies that directly compare phenotyping assays performed on the same samples. In a paper by Robert Shafer and colleagues, the performances of the PhenoSense and Antivirogram assays were compared using a retrospective analysis of phenotypic results recorded in the Stanford resistance database.

Phenotype sample results were selected from the database if they lacked any antiretroviral resistance mutations or if they contained a pattern of drug resistance mutations present in 2 or more isolates tested by each assay. Resistance mutation patterns were defined by 14 separate protease inhibitor (PI)-, 33 nucleoside/nucleotide reverse transcriptase inhibitor (NRTI)- and 15 non-nucleoside reverse transcriptase inhibitor (NNRTI)-associated resistance mutations. Sequences containing mixtures were excluded from the analysis. Sufficient susceptibility data was available for 15 of the 18 approved reverse transcriptase inhibitors and PIs.

The authors then analyzed what they defined as the precision of each assay: the median absolute

deviance from the median of susceptibility results for wild-type isolates and isolates with matching patterns of drug resistance mutations. The sensitivity of each assay was determined by calculating the proportion of isolates with antiretroviral drug mutations that had fold resistance exceeding the biological cutoff for each drug.

Several hundred results for each phenotyping assay were available for analysis. The authors first looked at isolates without drug mutations. Using their statistical analysis, they found that the median absolute deviance of fold resistance was significantly lower for the PhenoSense assay for all NRTIs except zidovudine (AZT, Retrovir) and for all PIs except lopinavir (LPV) and amprenavir (APV, Agenerase). For NNRTIs no significant difference in deviances between the assays was found.

Isolates with matching patterns of drug resistance mutations were then analyzed. The researchers again found that the median absolute deviance of fold resistance was significantly lower for the PhenoSense assay for all NRTIs except zidovudine and for the PI ritonavir (RTV, Norvir). There was no significant difference in deviances between the assays for the other PIs and the NNRTIs.

The authors further analyzed the sensitivity of each assay by looking at the fold change relative to the biological cutoff for each drug. In general, the biological cutoffs for the PhenoSense assay are lower than those for the Antivirogram assay.

The authors then looked at 3 common NRTI resistance patterns (M184V, M41L + M184V + T215Y, M41L + M184V + L210W + T215Y) and examined whether they would predict loss of susceptibility to lamivudine (3TC, Epivir), abacavir (ABC, Ziagen), stavudine (d4T, Zerit), didanosine (ddI, Videx) and zidovudine. There was no significant difference between the assays in their ability to predict levels of resistance for lamivudine and zidovudine. However, there were significant differences between the assays for the other 3 drugs. The Antivirogram tended to underestimate the loss of susceptibility for abacavir, didanosine and stavudine when the above mutational sets were present.

This study did not analyze the same samples prospectively in a blinded fashion using both phenotyping assays. However, the authors demonstrated that there are significant interpretative differences between these 2 phenotyping assays for some NRTIs, but that for most of the PIs and all the NNRTIs, the result was not significantly different. These assays are quite different in how they are performed, which could account for some of the greater variance seen in the Antivirogram with NRTIs. It is possible that samples examined by the different assays had different background polymorphic genetic changes in the *RT* or *Pr* genes. The authors attempted to correct for that in their analysis. Whether the decreased variance with the PhenoSense assay translates to improved clinical decision-making regarding the activity of certain antiretrovirals and, ultimately, clinical outcome remains to be seen.

A third type of assay, which combines information from genotyping and phenotyping assays, is called a virco®TYPE. This assay uses the *RT* and *Pr* gene sequence from an individual patient's sample to interrogate a database that contains over 30,000 matched genotypes and conventional phenotypes. It remains to be determined whether the virco®TYPE (virtual phenotype) from Virco, which provides a population estimate of fold change, will decrease or eliminate the increased variances seen with the Antivirogram for NRTIs.

Immune Reconstitution Inflammatory Syndrome and HAART

Shelburne SA, Visnegarwala F, Darcourt J, et al. *Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy****. AIDS. March 4, 2005;19(4):399-406.***

Although most people usually tolerate the initiation of HIV medications fairly well, some people can develop a significant inflammatory response that has been referred to as immune reconstitution disease (IRD) or immune reconstitution inflammatory syndrome (IRIS) after starting HAART. IRIS usually manifests as atypical presentations of known infectious agents, such as cytomegalovirus (CMV), Mycobacterium tuberculosis, Mycobacterium avium complex (MAC), or Cryptococcus neoformans. How often this syndrome happens or in what kinds of patients is still not exactly clear. A paper by Samuel Shelburne et al describes the frequency and patient-associated characteristics with which this syndrome develops.

This was a retrospective study that involved HIV-infected patients in Houston, Texas. Patients were included if they had been prescribed HAART and had follow-up CD4+ cell count and viral load results. In addition, trial participants had to have coinfection with Mycobacterium tuberculosis,

MAC or Cryptococcus neoformans, as demonstrated by a positive culture or a positive Cryptococcus neoformans antigen test from spinal fluid. The investigators decided for the purposes of this study not to include CMV disease. The definition of IRIS for this study was: receiving HAART, evidence of an inflammatory process not consistent with the usual course of an established infection or a new infection, a rising CD4+ cell count and falling HIV viral load.

A group of 259 patients was found to have coinfection with one of these agents. From that group, 180 (69.5%) met the final analysis criteria. IRIS developed in 26/86 with M. tuberculosis, 11/35 with MAC and 20/59 with Cryptococcus neoformans, or approximately 30% with each opportunistic infection. Thus, there was no difference in the risk of developing IRIS by underlying opportunistic infection.

The overall incidence of developing IRIS was 15.1/100 patient-years. For the 57 patients who developed IRIS, the median time between starting HAART and diagnosing IRIS was 46 days (range 3-658 days). The presentation of opportunistic infections during IRIS was most likely to manifest as localized lymphadenitis with tuberculosis and MAC and culture negative meningitis with Cryptococcus neoformans. There were no significant demographic differences between patients who developed IRIS and those who did not. There was also no difference in IRIS incidence according to the kind of HAART regimen the patients received (i.e., PI versus NNRTI). Patients who developed IRIS were more likely to be antiretroviral naive at the time that their underlying opportunistic infection was diagnosed.

At 3 interval time points over 9 months after starting HAART, patients who developed IRIS had significantly greater CD4+ cell increases and viral load reductions than those patients who did not experience IRIS. Patients with IRIS were more likely to have achieved an undetectable viral load (less than 400 copies/mL) and a sustained elevation in CD4+ cell count above 100 cells than patients without IRIS. Patients with IRIS were more likely to be hospitalized and undergo invasive procedures than those patients without IRIS.

This paper provides a relatively comprehensive description of the temporal aspects of IRIS after HAART initiation. About one third of the patients coinfected with these 3 opportunistic infections appear to develop IRIS. It appears that starting HAART during early treatment for these opportunistic infections results in a greater likelihood that IRIS will develop. In fact, the researchers found that the later HAART is started after successful treatment for opportunistic infections, the less likely IRIS will develop. This appears to be a double-edged sword, meaning that patients with active opportunistic infections who appropriately start HAART early during treatment for opportunistic infections, are more likely to have better CD4+ cell count and viral load responses, but greater morbidity associated with IRIS. Providers should be aware of the possibility that IRIS may develop in those patients with opportunistic infections who start HAART, as a delay in the recognition of IRIS could result in unnecessary workup and excess morbidity.

Drug Resistance as Measured by Single vs. Multiple Genotypic Tests Over Time

Harrigan PR, Wynhoven B, Brumme ZL, et al. *HIV-1 drug resistance: degree of underestimation by a cross-sectional versus a longitudinal testing approach****. J Infect Dis. April 15, 2005;191(8):1325-1330.***

Resistance to HIV medications has become a significant problem in the management of patients. As mentioned earlier, resistance testing, using either genotypic or phenotypic testing technologies, is now part of standard care. In most clinical settings, resistance test results obtained while a patient is on a failing HAART regimen have been used to make treatment decisions about what the next regimen should be. If patients have a long history of antiretroviral utilization and prior failure of these regimens, current resistance test results may not reflect all antiretroviral resistance that might be present. It is well known that many antiretroviral-associated mutations in the HIV-1 *RT* and *Pr* genes fade into the background quasispecies pool of viruses and are only maintained at a significant level for resistance assay detection if antiretroviral drug pressure is present. Thus, it might be useful to have as much information as possible on resistance at one's finger tips rather than just depending on the most current test result.

P. Richard Harrigan and colleagues conducted a study looking at whether a single genotypic resistance test or multiple tests across time was more predictive of total resistance burden.

The study was conducted at the British Columbia Centre for Excellence in Vancouver, British Columbia. Genotypic resistance testing was performed using a previously described assay and sequence results have been archived. This study analyzed the British Columbia Centre for

Excellence's database for patients who had 3 or more resistance tests between May 1996 and July 2004 (n=1,734 subjects; 11,404 genotypic resistance tests). They compared patients' most recent genotypic results to the results from all their historical genotypic tests. They also looked at whether patients were on an antiretroviral regimen at the time a test was performed. Major or primary mutations were defined using the IAS-USA list. The median time between the earliest and most recent test was 34.1 months. During that time, patients were prescribed a median of 5 different antiretroviral drugs. About 40% of the patients were not receiving HIV medications at their most recent test date and about 55% were on a HAART regimen. Over 90% of the patients changed some aspect of their antiretroviral regimen, with 4 being the median number of treatment changes.

The researchers found a general trend toward there being more primary mutations associated with patients' historical genotypic tests when compared to the current test result. For example, the prevalence of resistance-associated mutation M184V/I was 25.5% in the most recent genotypes and 58.8% in available historical genotypes. When all historical resistance test result mutational prevalence's were considered, 12.2% of the patients had resistance to 3 classes of antiretrovirals compared to only 4.5% if only the most recent test result was considered.

Looked at another way, 53.7% of the patients had no detectable primary mutations at their most recent visit compared to only 28.3% if providers considered all the patients' past genotypic test results. A greater discrepancy (or difference in the mutational pattern) between the most recent and historical test results was more likely to occur in patients who had more resistance tests ordered, had more antiretrovirals prescribed over time, had more time between resistance tests, and spent more time, in general, on antiretrovirals.

This study demonstrates the benefit of having, acquiring and retaining all resistance test results that a patient may have had. In addition, it is crucial to know a patient's complete antiretroviral history. Clearly, one cannot rely on just the most current resistance test result and antiretroviral regimen since this will underestimate the total resistance burden patients may carry, particularly if they are heavily antiretroviral experienced.

A Review of Interactions Between Natural Health Products and HIV Medications

Mills E, Montori V, Perri D, Phillips E, Koren G. *Natural health product-HIV drug interactions: a systematic review****. Int J STD AIDS. March 2005;16(3):181-186.***

Many HIV-infected patients use complementary and alternative medicine (CAM) as their only treatment or as supplemental care in addition to conventional HIV treatment and medications. Some estimates indicate that over 70% of HIV-infected patients in the United States have tried some form of CAM. Most of the herbs, vitamins and other alternative medicines that have been touted as having positive effects in HIV infection have not been rigorously studied in controlled clinical trials.

In addition, there is a concern that these various preparations may have significant drug interactions with conventional antiretroviral treatment or promote or create side effects or toxicities of their own, which then make it difficult to ascertain whether concurrent antiretroviral or other traditional medications might be the cause. A small number of studies have been performed with a limited number of natural health products and antiretrovirals that describe interactions, which might affect the efficacy of antiretrovirals. Mills et al performed a systematic literature review of the controlled trials that have been performed and which demonstrate whether there are any natural health product-antiretroviral metabolic interactions.

A thorough review of various scientific databases was conducted for both published and unpublished human clinical trials that examined pharmacokinetic interactions between natural health products and antiretrovirals. Two reviewers independently searched the databases and identified and reviewed the data.

Results showed that 84 potentially relevant abstracts were screened, but only 9 studies that met the criteria were included in the final analysis. The investigators have only reported on 5 natural health products. What they found was the following: There was no evidence of an interaction between milk thistle or goldenseal and indinavir (IDV, Crixivan); there was a significant interaction between garlic and PIs; there was a significant interaction between St. John's wort and indinavir; and there was insufficient evidence to define an interaction between vitamin C and indinavir.

This paper brings up several limitations in trial design and limitations of data interpretation. There was no standard trial design. In almost all of these studies, both the quality and potency of the natural health product was not controlled. In all of the studies that were included, the investigators only studied the interactions in healthy HIV-*uninfected* volunteers, and they only studied the natural health products with one antiretroviral.

In reality, HIV-infected patients may have different metabolic rates and normally would be on several HIV-related as well as other additional medications that could further contribute to the interaction potential with natural health products. Many of the studies also had a heterogeneous population, which could affect the results since drug metabolism and drug transporter genotype varies with gender and race.

The researchers evaluated the current literature that exists related to natural health products and antiretroviral interactions. However, the literature is sparse and of only fair quality and does not provide sufficient help to practitioners who need to decide how to approach the natural health products that HIV-infected patients may be taking. Clearly research is needed to make sense of the extent of interactions between currently used antiretrovirals and natural health products.

Nonetheless, it is clear that certain products, like garlic and St. John's wort, should be avoided, at least when taking HIV-1 PIs, as there are significant drug interactions resulting in significantly decreased PI levels that could compromise efficacy.

HIV and Hepatitis C Coinfection

Hershow RC, O'Driscoll PT, Handelsman E, et al. *Hepatitis C virus coinfection and HIV load, CD4+ cell percentage, and clinical progression to AIDS or death among HIV-infected women: Women and Infants Transmission Study****. Clin Infect Dis. March 15, 2005;40(6):859-867.***

Up to one third of HIV-infected patients are coinfected with hepatitis C virus (HCV). It appears that HIV coinfection results in increased progression of HCV infection as well as liver abnormalities and complications. Several papers have also described the effect of HCV coinfection on HIV progression. The studies, however, are split as to whether HCV hastens progression of HIV disease.

The difference in study conclusions is probably the result of differing study designs and types and the numbers of patients with coinfection that were studied. This study, by Hershow et al presents data from the Women and Infants Transmission Study (WITS) and asks the question whether HIV-infected women who are also coinfected with HCV progress more quickly than HIV-monoinfected women do.

The WITS cohort, which began enrollment in 1989, is an ongoing study in the United States of HIV infection among pregnant women and their infants. Women are followed during pregnancy and then every 6 months thereafter. The variables collected included, HIV treatment, HIV-1 viral load, CD4+ cell counts, urine toxicology for drugs of abuse and HCV antibody status. The main study outcome was HIV disease progression, as measured by CD4+ cell percentage, HIV viral load and one clinical outcome (time to AIDS-defining event or death). Questionnaires about recreational drug use were administered at each visit.

There were 819 participants enrolled between 1989 and 1995 with stored serum for HCV testing. A total of 202 women were excluded because they had AIDS before delivery or had HCV seroconversion during follow-up. The final analyzed group of 652 patients consisted of 29% HCV-infected women, 41% African Americans, 38% Latina and 15% white. The mean age was 27 years. Over 40% of these women reported recreational drug use during pregnancy. Women with HCV infection had similar CD4+ cell percentages and HIV viral loads at the time of delivery. Follow-up time was over 3 years. Thirteen percent of the HCV-infected and 21% of the non-HCV infected women were exposed to HAART.

In multivariable analyses, HCV-infected women had about a 2% higher CD4+ cell percentage and were not associated with a higher mean viral load over time. HIV treatment and CD4+ cell percentage were independently associated with lower viral load during follow-up. A total of 48 women progressed to AIDS and 17 died. HCV infection was not associated with a faster progression time compared to HIV-monoinfected women. A higher viral load close to delivery time was associated with progression, whereas a higher CD4+ cell percentage and HIV treatment reduced the chance of HIV progression. In all models, hard recreational drug use was not independently associated with HIV progression.

Thus, after controlling for CD4+ cell percentage, viral load level, recreational drug use and HIV treatment, it appears that in this cohort of young, predominantly women of color that HCV coinfection does *not* result in an increased chance of HIV disease progression. Differences in this study compared to other studies that have shown increased progression with HCV coinfection, include a younger population of only women, whose liver disease due to HCV may not have been as advanced, and a very high CD4+ cell count and percentage (500 cells/mm^3 and 30%, respectively), so the amount of HIV progression seen would be small. In addition, only a small percentage of women in this study received antiretroviral treatment or HAART. Other studies in the HAART era have shown increased progression in HCV-coinfected patients. Whether HAART treatment hastens liver disease in HCV-coinfected women and therefore results in increased progression will require further study.

Efficacy of Once-Daily Abacavir + Lamivudine + Tenofovir in Naive Patients

Khanlou H, Yeh V, Guyer B, Farthing C. *Early virologic failure in a pilot study evaluating the efficacy of therapy containing once-daily abacavir, lamivudine, and tenofovir DF in treatment-naive HIV-infected patients****. AIDS Patient Care STDs. March 2005;19(3):135-140.***

A lot of recent excitement in the field of HIV treatment has centered on class-sparing or once-daily dosing regimens. Triple-NRTI regimens, such as zidovudine/lamivudine/abacavir (AZT/3TC/ABC, Trizivir) or tenofovir (TDF, Viread) + didanosine + lamivudine, were thought to be potent enough as stand-alone regimens and were simple and convenient for patients to take. However recent data from several small and large clinical trials have demonstrated that triple-NRTI regimens may result in significantly more virologic failure than more traditional 2-class, 3-drug antiretroviral regimens.

A paper by Khanlou et al reports on a small study in which antiretroviral-naive patients were given a once-daily regimen of abacavir, lamivudine and tenofovir. The preliminary results of excessive virologic failure from this triple-NRTI drug regimen were originally reported last summer. This paper presents the more complete results from that pilot study.

This was an open-label, single-arm study in which patients were given abacavir 600 mg, lamivudine 300 mg and tenofovir 300 mg orally once daily. Patients were then followed for 24 weeks. Nineteen patients (3 women, 16 men) were enrolled. The median baseline CD4+ cell count and viral load was 277 cells/mm^3 and 147,167 copies/mL, respectively.

Genotypic resistance testing at baseline demonstrated that 6/19 had complete wild-type sequence, and 12/19 of the patients had polymorphic or secondary protease gene mutations and 8/19 had polymorphic or secondary RT mutations. Only 1 subject had primary NNRTI and NRTI mutations at baseline.

Adherence was measured by MEMS caps or pill counts. Adherence ranged from 92% to 100%. Seventeen patients completed more than 2 weeks of the study and were included in the analysis. Only 5 of 17 were considered responders. Twelve were considered nonresponders or had virologic failure.

The study was stopped early because of the high rate of virologic failure. The mean viral load decrease at week 8 was 2.7 $\log_{10}$ copies/mL. Nine patients had a virologic rebound between weeks 4 and 16. In the patients who did not respond and/or rebounded, 2 had wild-type virus, 5 had the M184V mutation indicating lamivudine resistance, 4 patients had the K65R + M184V mutations indicating tenofovir and lamivudine resistance, and none had K65R alone. All of the responders had baseline viral loads that were less than 100,000 copies/mL, whereas 8 of 12 patients with virologic failure had a baseline viral load greater than 100,000 copies/mL.

It is not clear why this triple-NRTI combination should have resulted in such a large amount of virologic failure. Neither adherence to the regimen nor side effects appeared to be an issue. Baseline antiretroviral resistance also did not appear to be an issue, although archived resistance mutations could not be excluded.

Abacavir was initially licensed as a twice-daily administered drug. But more recently, studies and subsequent licensure of abacavir/lamivudine (ABC/3TC, Epzicom, Kivexa) have demonstrated that abacavir and lamivudine can be effectively given once daily. Thus, with tenofovir already a once-daily drug, it stood to reason that these 3 drugs should be able to be given together as a single-

daily regimen.

Recent pharmacokinetic studies of abacavir and tenofovir have not indicated any significant drug-drug interaction, at least as measured by plasma concentrations. Whether there are more subtle intracellular interactions between these 2 drugs affecting their effective concentrations remains to be elucidated. This study concludes that this triple-NRTI combination cannot be recommended as a stand-alone regimen and thus practitioners should not prescribe this regimen to their patients.

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