SURROGATE MARKERS IN HIV / AIDS

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(Observed effects of The African River Pumpkin on surrogate markers)

a) CD4 cell counts
b) Viral loads

CD4 cell and Viral Loads are called surrogate markers since it is assumed that they are a substitute for AIDS or HIV.

Introduction

In the light of our observations and findings over a 6 months period in 60 HIV/AIDS patients, our view is that excessive reliance on these 2 surrogate markers in the disease is unhelpful in the management and care of patients. Our records show and suggest that a large number of patients may improve while these surrogate markers remain "abnormal". There appears to be no definite trend with regard to the levels of these surrogate markers during the period of treatment. Under the circumstances, continuing to rely on these expensive surrogate markers during the period of treatment (any treatment) runs counter to the principle of management of resources.[1] This practice is definitely not cost effective when carried out on a regular and frequent basis during the management of HIV/AIDS patients. The clinical picture and the subjective description by the patient appear to be more reliable when taken together.

In an attempt to seek clarification on the matter, it would be useful to review the literature by HIV/AIDS experts since 1984 to the present time. We choose 1984 since it was this year that HIV was "discovered" by Robert Gallo and Luc Montagnier

CD4 Cells: (CD = Cluster of Differentiation)

Although obvious, it needs to be stated that CD4 cells(formerly known as T cells) are not specific to AIDS. The lay public, and to a significant extent some health professionals as well associate the mere mention of CD4 cells with HIV/AIDS. This is unfortunate and it is the result of miseducation. 'Resistance to infection

may be decreased as a result of extremes of age, medical or surgical treatment or a combination of these factors'.[2]
All these are stressful conditions – psychological stress is another. All of these will lead to a low CD4 cell count in the individual affected. 'Several disease states cause a fall in CD4 cells. The most profound fall is in AIDS, but many severe illnesses will cause them to fall, including for example, measles.'[3]. CD4 cell counts are low in

- Medical or surgical stress
- Psychological stress
- Autoimmune diseases, e.g., rheumatoid arthritis
- Malnutrition & Poverty
- Tuberculosis
- Sarcoidosis
- Lymphoma
- Crohn,s disease
- Drugs: e.g., corticosteroids and cytotoxic drugs
- Transplant patients
- Alcoholic liver cirrhosis
- End-stage renal failure
- SLE

In 1981, James Goodwin wrote: ' It is starting again …….. The T- and B cell measures …… having run through the sick, the elderly, the young, the pregnant, the bereaved etc had finally run out of diseases. Each condition was the subject of many reports; so that now, to give but one example, we can conclude with some assurance that T-cell numbers are up,, down, or unchanged in old folks. And it is starting all over again, this time with T – cell subsets ….Sometimes the suppressor cell markers will be up and helper cells down; sometimes the suppressor cells will be down and the helper cells up; sometimes they will be unchanged … My strongest argument is this: Measurement of T and B cells and their subsets in diseases has no clinical meaning.'[4]

The largest clinical trial ever which evaluated AZT was highly critical with regard to CD4 cell counts as a marker of improvement or disease worsening amongst trial subjects. The authors concluded that: 'The small but highly significant and persistent difference in CD4 count between the groups was not translated into a significant clinical benefit. Thus, analyses of the time until certain concentrations of CD4 were reached (e.g. 200/□L, 350/□L, or 50% of baseline) revealed significantly shorter times in the Def(erred) group. Had such analyses been regarded as fundamental, the trial might have been stopped early with a false positive result. This discrepancy in the differences between Imm(ediate) and Def groups in terms of changes of CD4 count and long-term clinical response casts doubt on the uncritical use of CD4 counts as "surrogate endpoints" in trial.[5]

Writing in a journal of statistics in 1994, Fleming stated: "It is very apparent one cannot simply consider establishment of statistically significant treatment effects on CD4 cell counts to be a valid surrogate for either of the two clinical endpoints.

When the progression to AIDS/Death endpoint was positive, the CD4 endpoint appropriately was significantly positive in 7 of 8 trials; unfortunately however, the CD4 endpoint was significantly positive in 6 of 8 trials in which the progression to AIDS/Death endpoint was negative. The relationship of CD4 effects and survival is even more unsatisfactory. The CD4 endpoint was significantly positive in only 2 of4 trials in which the survival endpoint was positive; yet it was significantly positive in 6 of 7 trials in which the survival the survival endpoint was negative. In three other trials, survival trends were observed which were in the opposite direction of significant treatment effects on CD4."[6]

The PCR & Viral loads

With the passage of time, HIV/AIDS scientists began to doubt the clinical significance of CD4 counts – this they did reluctantly. Reliance on CD4 cell count was replaced by the PCR viral load test as the primary surrogate marker to be used in ARV clinical drug trials. Unfortunately, The PCR also has its own serious problems. Researchers from The Massachusetts School of Medicine concluded: "Plasma viral load tests were neither developed nor evaluated for the diagnosis of HIV infection …. Their performance in patients who are not infected with HIV is unknown and their use leads to misdiagnosis of HIV infection.[7]. Researchers at the prestigious institution – Institute de Salud Carlos III say the following regarding viral load measurements: "Since their specificity is not well known, these tests must not be used for diagnostic purposes."**[8]** **Roche, the manufacturer of PCR has the following insert warning the user: "The Amplicor HIV- 1 (RNA) Monitor test is not intended to be used as a screening test for HIV-1 infection.(Roche Diagnostic Systems Amplicor HIV-1 Monitor Test package insert, PMA No. BP950005/4).**

Conclusion

With this information, and mounting current evidence from observed studies and clinical trials, we would suggest that a great deal of caution be taken when ever CD4 cell counts and viral loads are being looked at. We strongly feel in the light of the evidence that the frequent requests and references to CD4 cells and viral loads are not a cost effective way of looking after immuno-compromised patients. Our view is that less reliance is placed on these two surrogate markers but instead more reliance should be on the patient's story and the clinical picture with regard to whether or not there has been an improvement.

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