West of England Medical Journal

Formerly Bristol Medico-Chirurgical Journal

The e-journal of the Bristol Medico-Chirurgical Socie

WEMJ Volume 110 Number 2 Article 1 March 2011

Therapeutic Vaccines for HIV and Cancer

The Long Fox Memorial Lecture

presented to the Bristol Medico Chirurgical Society at Bristol University 10.11.2010

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INTRODUCTION

The general public recognises that a vaccine is something that one takes in order to prevent getting an infectious disease later. In this regard there is much publicity about the benefits of having specific flu vaccines. Although dramatically effective in acute diseases, it is becoming evident that this concept of vaccination is much less effective with regards to chronic diseases, such as human immunodeficiency virus (HIV) and Tuberculosis.

Several cancers have clearly been linked to viral causative agents, such as cancer of the liver to Hepatitis B virus and cancer of the cervix to human papilloma virus. These can both be vaccinated against and hence classical prophylactical vaccines can indeed greatly reduce the cancer incident and deserve to be recognised as effective cancer vaccines.

However, the majority of cancers are not caused by infectious agents but are recognised to be susceptible to the immune response. There has therefore been a longstanding attempt to try to induce a favourable immune response that should be able to reject cancers or, indeed, residual cancers after they have been removed or treated to prevent them occurring. It is therefore very much a therapeutic vaccine approach. More recently, this approach, which is fairly standard in cancer research, has been applied to infectious diseases and there is a new interest in developing therapeutic vaccines for HIV and other diseases, which would be given after infection in order to prevent disease. As such, these therapeutic vaccines are vaccines that prevent disease and not infection.

THE PROBLEM WITH HIV VACCINES

I first started working with HIV shortly after it was discovered in 1984 and described the CD4 as a receptor and the various neutralising antibodies induced by the virus in patients. Following publicity about our work, I was asked how long it would take to have an effective vaccine for HIV and, not knowing, I took advice and was told between six and twelve months! Over a quarter of a century later we still do not have an effective vaccine. There are many reasons for this. First of all, the virus is very, very variable and there are many different strains. Secondly, it enters the body like a Trojan horse and being present inside cells can evade specific vaccines against it.

Whilst researching longitudinal studies of patients and neutralising antibodies it became clear that there were some patients who progressed very quickly to AIDS and others who appeared not to progress at all. Also, attempts to use the chimpanzee to help develop an HIV vaccine was thwarted by the fact that however much virus the chimpanzee had, he never got AIDS. I and colleagues from the European network put together a consortium to document the determinants of infection and disease. The results were initially unexpected but in retrospect, not surprising. It appeared that in order to develop AIDS the body needed to have a markedly activated immune response. Indeed, whatever way the data was looked at, it was clear that without the activation against the virus there would be no progression to disease and this was confirmed in the chimpanzee.

We then asked the basic question as to what causes the pan-activation of the immune system, seen in patients progressing to AIDS. After consulting many famous immunologists it appeared that there was a shortlist of only three. The first was the viruses variability, leading to constant new stimulation against new epitopes, the second was the presence of super antigens, like the tampon toxic shock syndrome, and the third was the reaction against foreign cells, such as the graft versus host disease seen in transplants. Most virologists and, indeed, immunologists, thought the most likely explanation was the former but this does not explain why the greatest virus variability is seen in the long term non progressors, suggesting that it is a function of time, as opposed to cause of activation. The second cause, the super antigen, was initially published in Nature and Science as the likely cause but we and others have shown that the data was superficial and the effects attributed to a super antigen were more than one would expect with a deteriorating immune response. This left only a graft-versus-host-like syndrome, which can occur acutely or chronically. Indeed, HIV infection mimics the chronic graft versus host disease so perfectly that others have mentioned the similarities clinically and patients with chronic graft versus host disease have been used to demonstrate the features of HIV infection when no appropriate patient is available.

In order for HIV to cause a chronic graft-versus-host-like disease it would have to have some similarity to the molecules which induce this. The widely available sequencing data showed that there were several regions of homology, which were recorded but ignored on the grounds that the sequence homology wasn't one hundred percent. As more and more sequences from different viral strains came out it was clear that these HLA regions were completely conserved and that any amino acid changes noted completely conserved the structure.

We then published a large number of papers showing that a fifth and final conserved region of the outer envelope could bind peptides exactly like the transplant antigens, HLA. Moreover, we demonstrated that this region could present peptides in the appropriate context and that cells presenting the peptide of this region could be killed by T-cells primed with foreign HLA. These studies showed clear cross reactivity between the virus and the human leukocyte transplant antigen (HLA).

Having identified this region we then looked at the serum from patients who had been infected for years but did not progress to AIDS and noted that these patients have high antibodies to this region. It was interesting that these antibodies are not neutralising in the classic assays that virologists use. It did, however, suggest that perhaps these antibodies were important in preventing disease progression and if the host was seeing the virus in a similar manner to foreign HLA then this would induce the immune response that would ultimately lead to AIDS.

The best data on this was published from the Walter Reed Army Hospital in Washington which followed large cohorts of patients who were infected with HIV. Of the thousands of variables they monitored they came up with only two conclusions. The first was that the main neutralising region correlated in a completely opposite way from what was expected, in that the patients with the highest titre of antibodies to this region developed AIDS quickest in the absence of therapy and that the patients with the highest titres to the non neutralising C5 regions live the longest without disease. As all initial vaccine attempts were made to mimic the neutralising epitope and induce high neutralising antibodies, this would explain why the vaccine was not only doomed to failure but also why two studies were stopped early because it looked like the vaccine arms were doing worse than the control.

We therefore proposed the idea that this C5 region would make a very good vaccine to give people who were infected with HIV and whose immune system was partially restored with the highly active anti retroviral drugs or HAART, as it is known. After years of having this ignored and grants turned down it was heartening to find I was able to propose it as an extension to a project with colleagues to the Norwegian Research Council, who agreed to fund this approach into the clinic. We have now identified good peptide candidates to mimic this region and are optimising them for the best adjuvant to combine with. As soon as this has been optimised we have the funds and will go ahead to an early phase I trial in the clinic, after which we hope it would be made available by one of the larger agencies for large scale therapeutic studies.

The concept that there can be part of a chronic infectious agent that stimulates the immune response into over activity that does not kill the agent, but rather fuels it, could be applied to a large number of other chronic agents, such as the Hepatitis C virus, which is very hard to neutralise, and to malaria, dengue and tuberculosis.

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CANCER VACCINES

The first scientific observations that put the concept that the immune response may be able to eradicate cancer firmly on the map were made at the turn of the last century by the New York surgeon, William Coley, who noted that patients who became infected before or after operations often became free of tumour. He deliberately, therefore, took certain patients with tumours and induced infections but as there were no antibiotics the results were sometimes fatal.

He therefore mimicked the infection by making preparations of bacterial cell wall and injecting these into the patients to induce a pseudo infection and this mixture became known at Coley's toxins, eponymously named after the New York Surgeon. It would appear that this work was hard to reproduce and that the details were very important and that the discovery of radiotherapy sidelined further progress in this area when Coley retired.

Since then there have been many attempts to stimulate the immune system to induce a response against cancer cells and there are many anecdotal reports on this using a variety of non specific stimulation agents, such as BCG. Indeed, installation of BCG into the bladder has been shown to be more effective at inducing a complete response than chemotherapy. This certainly would appear to work in a similar manner to Coley's toxins, as the BCG induces an acute inflammatory response in the bladder, which leads to the tumours disappearing on resolution.

Over the last few decades there have been numerous attempts to develop therapeutic cancer vaccines. They have largely been focused on the non specific agents, such as BCG, used initially alone and then as adjuvant to tumour antigens, supplied usually in the form of autologous tumour. Indeed, the first two reports of randomised studies showing a clinical benefit in favour of the vaccine were both in autologous vaccine preparations in renal and colorectal cancer. Both these reports appeared in the Lancet a few years ago.

Unfortunately, autologous tumour vaccines are very bespoke and difficult to prepare and do not fit into the way the EU clinical trials directive has been (mis) interpreted.

It was shown by Donald Morton and my own laboratory that allogeneic cells were not only a much more practical way of presenting numerous cell antigens but could also induce a stronger immune response because of the foreign component acting as a stronger adjuvant. Moreover, these cells could be reduced to cell lines and mass produced for vaccines. Unfortunately, although there have been great responses in small studies in anecdotal situations, trials in melanoma and prostate have been disappointing in trials in multi centre phase III situations.

TECHNOLOGY

While these studies were going on and, in particular, good phase II data being produced with the cell line approach, other people started to develop vaccines on a more sophisticated basis. There are now numerous approaches which have been tried in the clinic and these include peptide based vaccines, protein vaccines, mucine based vaccines, ganglioside based, DNA based, RNA based, molecular engineered epitopes with cytokines and viral vectors, etc. Interestingly, they have been tried in a wide variety of tumour types and very similar data to the early cell based studies has been noted, namely good phase II studies in a single centre, with the benefit being lost when multi centres and large numbers are used.

Why do phase III studies not reproduce the good results seen in single centre, non randomised situations?

My own group has been particularly fascinated by this ever since I went to help a multi centre trial recruit patients and noted the very poor quality of patients being put forward for the trials in other centres. To put it bluntly, most phase II studies encourage patients' enthusiasm and the volunteers to the trial tend to be very fit and health conscious, on special diets and supplements and regular exercise. The patients I saw being enrolled at the different centres couldn't have been more different, often being obese, heavy smokers with poor nutrition and probably a total absence of exercise.

We therefore looked at our own studies and took serum samples from the patients who clearly progressed very quickly and those who survived longer than expected and put them through a proteomics programme to look at any difference between these groups. What we saw was surprising in that there was no clear pattern for the good responders but there was a pattern for the poor responders, in that they all had excess of proteins associated with inflammation. Since we did this there are two other large randomised studies which have noted that if patients with a particular inflammatory marker are removed then the trial shows benefit in favour of the vaccine. Had these patients not been included in the first place then the trials would be clearly positive and probably the vaccines registered.

The finding that elevated inflammatory markers are associated with poor prognosis should not be surprising, in that chronic inflammation causes immune suppression, which is a basic tenant of the immunology of wound healing and nicely links the observation made over one hundred years ago that cancers are wounds that will not heal. This therefore raises the potential of anti inflammatories in conditioning patients prior to vaccination and this is a very interesting area in which an Italian group have already published that anti-inflammatories, given with a vaccine in mice, give better outcomes than those with the vaccine alone.

FINALLY, SUCCESS AT LAST!

Many of the phase II studies, done in a variety of tumour types, not just melanoma where nearly all the early trials were focused, show variable response that is lost in phase III studies. One of these trials was the use of specially prepared dendritic cells from the patient, expanded and mixed with antigen before giving back to the patient, with prostate cancer. The vaccine was prepared in patients with late stage disease and the early indicators of efficacy, such as prostate-specific antigen (PSA) drop and time to disease progression, were not seen in the larger studies.

This vaccine was promoted by an American company, called Dendreon, who had access to very deep pockets and were able to keep the trials going to survival, where two studies showed benefit in favour of the vaccine, albeit small but significant. The confirmatory trial designed to test this, again, was positive and Dendreon have the honour of being the first company in the world to produce the first therapeutic vaccine for use in human cancer, called Provenge.

However, the inflammatory aspect again probably comes into interpretation of these studies, as nearly all these patients have had chemotherapy prior to the vaccine, or afterwards and I would suggest that the real result of the trial is that the vaccine, plus chemotherapy, gives a survival benefit over those who just have chemotherapy alone. Therefore this vaccine is the first to get recognition and registration by the FDA for humans.

I was subsequently to understand, however, that in the cancer vaccine stakes it had been pipped at the post by a vaccine for melanoma in dogs. Melanoma developing in the inside of the upper jaw is very common in dogs and is lethal. Because of the melanoma model, a DNA based vaccine was produced and shown to delay disease progression in a non randomised study, which was compelling enough for the vaccine to be licensed for dogs with this condition! At a meeting when this was presented, one of the eminent vaccine researchers said he had concerns about the ethics of consenting this study, whether it was a bark or a wag of the tail. I commented I was far more concerned about the poor (paw) marks on the quality of life forms!

THE FUTURE

Behind Dendreon are several other vaccines in randomised trials. My own company, Onyvax, had a cell based vaccine for prostate cancer, which had wonderful results in our institution but failed to give the early signs of efficacy in a big multi centre study and was unfortunately backed by 3i, who did not provide the money to get the survival data and pulled the plug. This was a tragedy as there was already a survival split earlier than on the Dendreon study in the same group of patients. This is a very good indicator that the endpoints are different in biologicals and there is a learning curve as they are developed.

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There are a number of vaccines now in trial and I am aware of another prostate vaccine which appears to be as effective as the Dendreon one and does not rely on bespoke production. It is interesting to note that the price for the Dendreon prostate vaccine is $93,000 for a course! There are also two vaccines for lung cancer, both of which have encouraging survival trends, as well as one for lymphoma.

The future is combined therapy. One of the things that has become clear with the development of cancer vaccines as therapy is that patients who have been on vaccine programmes give the impression of responding better to other treatments, when necessary. Patients who have had vaccination, who have had radiotherapy, often have dramatic and unexpected responses. Similarly, it has been noted that vaccination may enhance the response to chemotherapy and, at the very least, reduce the side effects of chemotherapy, as noted in a randomised study of a Mycobacterium vaccine in lung cancer patients.

This suggests that the earlier in the treatment programme the vaccine is given, the better the possible outcome. In the case of prostate cancer, this is certainly likely to be true as the National Cancer Institute have shown in a randomised study that patients who have vaccines before endocrine treatment do much better than the other way round.

HOW OTHER THERAPY CAN ENHANCE THE RESPONSE TO VACCINES

It is clearly established in the literature that all types of immunotherapy seem to enhance the effects of radiotherapy. However, it also appears to be true that to give immune responses after radiotherapy can lead to a better outcome. There would appear to be a favourable reaction with the cell killing caused by the radiotherapy and the stimulated immune system, along with the possibility that radiotherapy damps down the suppressor activity from the tumour and the invasive suppressor network.

To our surprise, it also appears that there a number of drugs that are also able to do this and therefore lead to a better response to vaccination than vaccination alone. Amongst these drugs are some well known agents, such as Gemcitabine, used for pancreatic cancer and lung cancer, which is able to kill the infiltrating myeloid suppressor cells that protect the tumour from an otherwise effective immune response. Additionally, a number of well known agents in low doses, as opposed to high doses, inhibit suppressor T-cells, and these include Cyclophosphamide and Vinorelbine.

INFLAMMATION, ANGIOGENESIS AND IMMUNE STIMULATION – THE GOLDEN TRIANGLE

As previously mentioned, whereas acute inflammation can lead to a cytokine storm and clearing of residual tumour, chronic inflammation leads to enhanced angiogenic factors and immune suppression. Therefore, in chronic disease with an inflammatory component, which is essentially most cancers, an optimal treatment plan would be to target inflammation, anti angiogenesis and to boost the immune system. I will now discuss a group of agents that have all these properties.

THALIDOMIDE AND ITS ANALOGUES

The history of Thalidomide is well known. Based on a glutamic acid, which is an essential amino acid, its modified structure was introduced as an ideal sedative for pregnancy. The birth defect association was a total disaster which led to its demise. However, investigators in Israel had noted that patients who had been taking it with chronic skin conditions, such as Leishmaniasis or Leprosy, appeared to have clinical benefit. It was thought to be having a marked anti inflammatory activity and was cautiously used in selected centres for certain auto immune diseases where it was noted to be more effective than steroids.

My special interest in this drug occurred when I was consultant on call and a patient with severe Bechet's syndrome was a tertiary transfer from another hospital because of the total failure to respond to steroids. Bechet's involves ulceration of the mouth, genital and peritoneal regions. In this case, the patient was so severely ill that she had been on a drip with steroid injections for several days. I confirmed with a colleague that the only thing worth attempting was Thalidomide and that this would have to be crushed and squirted down the back of the throat as it is notoriously insoluble and cannot be given intravenously. In less than twenty four hours all these lesions had completely healed and the lady was eating and drinking normally.

I was aware of similarly dramatic improvements in autoimmune skin conditions at this time. However, not only was there a problem with birth defects but serious neuropathy curtailed any long term use of this agent. At the time I was working for the MRC at Northwick Park and had established a good relationship with Glaxo, down the road in Greenford. I suggested that we take the Thalidomide back-bone and make analogues of it to see whether we could enhance the good properties and, hopefully, reverse the birth defect one. I thought it was a small chance that the two properties were separable but thought it worth doing. Initially Glaxo showed interest but the legal department prevented any further progress.

I wrote a paper in a trade journal out of frustration, thinking that would be the end of it. A few weeks after it was published I was contacted by Steve Thomas from Celgene who wanted to come over and discuss a collaboration in order to develop Thalidomide. He had just joined a small spin-out company, which was essentially a start up biotech company called Celgene in the United States with very few employees and no products. To cut a long story short, we agreed to put Thalidomide into HIV patients in the clinic, where it was dramatically effective at curing their chronic diarrhoea and skin conditions. On these grounds we proceeded with an analogue programme.

After trying several of these analogues, one was particularly interesting to put into the clinic, indeed, I had the honour of giving Revlimid/Lenalidomide, as it is now known, to the world's very first patient on an informed consent basis. During the development of Revlimid/Lenalidomide, it had become clear that Thalidomide was effective in multiple myeloma. The patient being described had myeloma that responded to Thalidomide but he had developed terrible neuropathy. He was transfusion dependent four times a week and I gave him the Revlimid daily for a period of three weeks, in the first instance. However, by the middle of the second week he was no longer transfusion dependent and felt dramatically better. He therefore went home, back to the States, and I was to meet him fit and well, still on Revlimid, two and a half years later.

We have subsequently done a lot of work on Revlimid, both in the clinic as well as preclinically and it is clear that it has strong anti inflammatory properties, is an anti-angiogenic and is a co-stimulatory agent, so much so, it enhances the effect of vaccines. We first showed this in mice, in a tumour model and published this is the Journal of Immunology in 2002 but no notice was taken of the claim that this drug could boost vaccines until very recently when it has become clear that patients on Revlimid with myeloma actually make an immune response to the pneumococcal vaccine, which they previously have not when on other treatments. We have now finally written the protocol, which we hope will be the first of several, that will have Revlimid as an oral adjuvant to a vaccine. The first study is in myeloma patients who are on Revlimid but in stable disease with markers outside the normal range. It is hoped that adding a vaccine into such a scenario in chosen myeloma patients will lead to clinical improvement.

CONCLUSIONS

In a few short years we have gone from the concept of therapeutic vaccines as unthinkable to the registration of the first one for cancer in humans. Not only will this be the first of many but the clear indication is that benefit can be greatly enhanced by combining it with more conventional treatments, as well as some of the newer drugs, such as Revlimid. This has opened up the possibility of therapeutic vaccines being used in a number of chronic conditions. As well as HIV, several infectious agents are logical targets, such as HCV, HPV, EBV, malaria, dengue, tuberculosis, etc. More surprising is that the concept of therapeutic vaccination to alter abnormal immune networks means that many other chronic diseases are being targeted for this approach, including hypertension, diabetes, myelitis, heart disease, tobacco and drug addiction, as well as dementia, such as Alzheimer's.