Drug Treatments on the Horizon – Clinical drug studies in NF

By Susan Conradi Toomey, MS

More so than ever before, treatments for the neurofibromatosis disorders are being studied with an optimistic eye toward medications that can reduce or eliminate certain symptoms. In the last decade, and the last few years especially, the role of drug trials in neurofibromatosis 1 (NF1) and neurofibromatosis 2 (NF2) has become a reality. (Currently there is no treatment or drug for the newly recognized form of NF called schwannomatosis, however funding is underway to quickly advance the understanding of that disorder.)

Many of the drugs currently being studied however are not very familiar to the majority of families dealing with NF. Beginning with this newsletter, we will be introducing drugs that have shown promise as treatments in the neurofibromatosis disorders. Some of these drugs may very well live up to their potential becoming household names for those living with NF, while other drugs may show that they are not suited to the unique challenges of the NF disorders.

We will begin our series by taking a look at the drug sirolimus; also known as rapamycin and Rapamune (its trade name). The drug is currently being studied for its potential to slow or stop the growth of tumors (specifically plexiform neurofibromas) in NF1.

Sirolimus in NF1

Sirolimus is a relatively new drug which interestingly was isolated in the 1970's from a fungus on Easter Island. The drug acts as both an antibiotic and as an immunosuppressant. As an antibiotic, sirolimus blocks a protein involved in cell division and as an immunosuppressant, the drug stops the growth and function of certain cells of the immune system. One of its initial and ongoing uses was to prevent the body's rejection of organ and bone marrow transplants.

Currently, Sirolimus is being tested in drug trials in several types of cancer for its anti-tumor activity, and has shown success in the treatment of certain tumors in tuberous sclerosis. It is also being considered in the treatments of individuals with Huntington disease and for symptoms of autism.

In NF1, sirolimus is being studied for its ability to slow or stop the growth of plexiform neurofibromas (PNs). Up to 1/3 of all individuals with NF1 will experience a plexiform neurofibroma, one of the most troublesome and invasive tumors. PNs can cause a variety of problems including pain, disfigurement, and tend to spread into surrounding tissues and organs with web-like protrusions. And while not likely, a small percentage of PNs can become malignant. Surgery is currently the only treatment, however many PNs are not candidates for

surgery due to how they have spread and infiltrated the surrounding tissues. Thus, finding a way to slow or stop the growth of these tumors is a primary concern for patients and the doctors who treat them.

To understand just how sirolimus works against the PN tumors, it is important to understand how those growths begin in the first place. The gene for NF1 codes for a protein called neurofibromin. In our bodies, our cells like to grow and divide and are often happy to just keep multiplying. When neurofibromin is present (in individuals who do *not* have NF1) it helps in a number of "pathways" that put a "brake" on cell growth making tumors (including PNs) much less likely to develop and grow. Individuals with NF1 have a decreased amount of neurofibromin in the body. For them, the pathways that are supposed to stop cell growth are disrupted, making PNs and other growths much easier to develop.

One of the first "pathways" in NF1 to be studied (and according to scientists the most logical place to start) was the RAS pathway. Research, however, showed only limited success in finding drugs which would inhibit the RAS pathway. Another pathway affected by the absence of neurofibromin is mTOR, a pathway which has a number of functions in the human body important for cell growth and proliferation. In individuals with NF1, the mTOR pathway is over-activated. The drug sirolimus works by reducing the activity of the mTOR pathway thus reducing or stopping the runaway growth of cells in a PN. In other words, sirolimus helps put the "brake" back on by slowing or stopping cell growth.

Several years ago, as scientists were studying the tumors of NF1 mice, the mTOR pathway was uncovered, leading to the pleasant surprise that a whole class of drugs (including sirolimus - already in use for years), could be a possible treatment for NF1 tumors. This knowledge led to the initial trials of sirolimus in NF1 patients. Fast forward to 2008 and a phase II trial is currently getting underway to study just how well sirolimus works in treating non-operable nonmalignant PNs in humans. In studies being funded by the US Army and Department of Defense (through the Congressionally Directed Medical Research Programs - see sidebar), the scientists at the University of Alabama Birmingham along with 8 other NF Consortium members will focus on the effectiveness of sirolimus. The trial is open to children aged 3 or older, and adults, with plexiform neurofibromas which are growing. Selected patients will be given the drug twice daily by mouth on a daily basis. Radiographic studies (MRI) will be done to document tumor growth or regression. The studies will take several years to complete, but preliminary results of the sirolimus drug trials thus far have been optimistic. See the resources box below to find out more about this study.

In this exciting new era, as scientists and physicians move forward with their understanding of NF1, NF2 and schwannomatosis, drug trials are progressing toward viable treatments for some of the symptoms of NF disorders. Stay tuned for future newsletters in which we will look at other drugs that are currently being investigated for their effectiveness in the treatment of NF symptoms.

Why is the military involved in the funding of NF research?

Actually, the Department of Defense (DOD) has a long history of medical research dating back to the early 1800s when open war wounds were used to study biological processes and helped to develop new surgical treatments. Over the years the medical teams of the military branches have developed important vaccines, antibiotics, blood products, prosthetics, and advances in hygiene.

Beginning in 1992, through annual Congressional legislation, the Department of Defense (DOD) funded the Congressionally Directed Medical Research Program (CDMRP) with the US Army managing and overseeing much of the research. The mission of the program is to promote research toward the understanding, diagnosis, and treatment of specific disorders to enhance the quality of life for those with the disease. The CDMRP has supported NF research since 1996 with a total of $182 million (from 1996-2007). This funding was continued for 2008 with an appropriation of $8 million for a variety of research awards.

Of those DOD research awards, doctors at University of Alabama Birmingham received 5.7 million to study and test new treatments for NF. This award will be shared among the 9 NF Consortium members, who will focus much of their efforts on the clinical drug trials of sirolimus.

Resources:

More information about the sirolimus trial can be found online at www.clinicaltrials.gov – the clinical identifier is NCT00652990.

The University of Alabama at Birmingham which is coordinating the study has a useful web page about the trial at www.genetics.uab.ude/NeurofibromatosisClinic-ResearchSirolimus.html

Additional information on this and other drug trials for NF can be found at www.ctf.org under the Research tab.