Sharing Knowledge, Supporting a Cure

Sept. 22, 2006
Volume 1, Issue 1

mpd-support

Inside this issue:

Time to rethink the MPD paradigm?

Tall, lanky, with closely cropped hair and rectangular glasses, Professor Tony Green speaks precisely about his research and sensitively about the welfare of his patients. His voice betrays just a bit of nervous energy as he talks about new discoveries in the MPD world – he is clearly thrilled about the latest advances.

Professor Green trained in medicine and haematology at Cambridge, London and Cardiff, and completed his post-doctorate at Royal Melbourne Hospital, Australia. He has since established one of the leading academic haematology departments in Europe, and made several seminal contributions to research in this area. Speaking to the MPD patient support group this June, Professor Green explained how our understanding of myeloproliferative disorders has evolved. Over the last fifty years, there have been a number of landmark observations about MPDs, but despite the best efforts of many investigators, understanding how these diseases work remained frustratingly elusive.

"That all changed in a dramatic way last spring," Professor Green explained, "with the publication of four papers within a matter of weeks, all of which identified a unique acquired mutation in the cytoplastic tyrosine kinase JAK2. In the past eighteen months

Professor Tony Green

we've made spectacular advances in our understanding of MPDs."

How does JAK2 work?

Our bone marrow contains a progenitor, or in other words a base or "stem cell." The stem cells... *(article continues P2)*

Raising funds for MPD research

Congratulations to our runner Chris Cross, who raised £1500 for MPD-Support , shown here sporting her London Marathon medal! Many thanks as well to Hira Sisodia, MBE and the Royal Kingdom Charity for organising a charity dinner at Imli Restaurant in Leicester, which raised £500. Dr. Deepti Radia spoke at this event and launched the MPD-Support Charity. Thank you to our fund-raisers! Monies raised will go toward funding MPD-

Support's website and new publications.

What JAK2 testing means for patients:

1. The JAK2 test provides a much faster way to diagnose MPDs.
2. Knowing a patient's JAK2 status may help doctors understand which therapies to prescribe.
3. In the longer term, we may be able to develop designer drugs to block the mutant JAK2, and hopefully halt the disease.

Missed Professor Green's presentation at the June 2006 MPD-Support meeting? You can also view an internet video of his presentation to the European Haematology Meeting: go to.http://congress.ehaweb.org/11th/ and click on Plenary Session I.

Rethinking the MPD paradigm... *(article continues from P1)*

in our bone marrow can grow and mature into red blood cells, white blood cells or platelets. For example, the stem cells in the bone marrow of a healthy person grow into red cells in response to a hormone called erythropoietin (EPO). JAK2 is a vital part of a communications pathway that allows the EPO hormone to send a message to the stem cells. The hormone travels through the bloodstream; when it reaches the stem cell, it locks into a receptor site on its surface, which then in turn locks onto the JAK2 molecule inside the cell. This changes the structure of the JAK2 molecule, so that the JAK2 can transmit the message forward to other proteins on the communications pathway.

Many patients with MPDs develop a mutation in the JAK2 protein. The mutation changes the way the JAK2 operates: the JAK2 doesn't simply transmit a signal in response to the EPO hormone, but instead acts on its own, amplifying the signal from the receptor. Professor Green believes, "If we were able to develop a drug that would 'patch up' the receptor site on the mutant JAK2, it would stabilize the whole molecule." This type of designer drug could potentially halt myeloproliferative disease in patients with the JAK2 mutation.

A entirely new way to view MPDs

Professor Green wonders if it's time to challenge the MPD paradigm, and rethink the way we classify *(cont. P4)*

Act fast and recognize a stroke

Many MPD patients are at risk of suffering a stroke, and some of us have even experienced one. But we don't always know what we could expect if we had a stroke. The word "stroke" itself is frightening, but the damage to the brain caused by strokes can be significantly reduced by acting fast. Here are some of the signs of strokes to help you and your family recognize what is happening:

- Sudden weakness or numbness of face, arm or leg, especially on one side of the body (the most critical symptom);
- Sudden confusion, trouble speaking or understanding;
- Sudden trouble seeing in one or both eyes;
- Sudden trouble walking, dizziness, loss of balance or coordination.

Strokes can be indicated by any of the above symptoms in mild, moderate or severe degrees, and in any combination. If you think someone is having a stroke, If a person shows any of these symptoms, it's important to get them to A&E immediately. Strokes can be treated and the outcome can be very good, but it's essential to take fast action. □

"The word 'stroke' itself is frightening, but the damage to the brain caused by strokes can be significantly reduced by acting fast."

Top Tips

Here are some top tips on managing MPDs and medications. Please email your top tips to us at info@mpd-support.co.uk!

- Itchy skin is a common symptom of MPDs. One remedy that works well is to use an emollient cleanser (like E45) instead of soap, and to use a medicated shampoo (e.g. Polytar). If you feel especially itchy after a bath or a shower, try wrapping up warm after drying - sometimes it's the cooling down that triggers the irritation.
- If you feel tired or sleepy on taking hydoxyurea, try taking the tablets before you go to bed—they do not need to be divided during the day.
- If you suffer palpitations after taking anagrelide (Xagrid), divide the doses up through the day, and avoid caffeine (coffee, tea, diet coke). It also helps to avoid exercise for about an hour after taking them. □

Healthy Living with MPDs

Many MPD patients suffer from fatigue, due to their illness or due to their medication. One way for patients to feel better and have more energy is simply to eat a balanced diet and to exercise regularly.

There are lots of easy ways to improve your diet. It's important to eat five fruits and vegetables every day, and you can see if your diet includes everything you need by keeping a food diary. Another way to improve your diet (and save money too!) is to have a vegetarian day two or three times per week. Some great low-fat choices are black bean soup, stir-fry vegetables with tofu, or pasta with tomato and chick pea sauce. All of these are fast and easy to make. Add a salad and a piece of fruit, and you'll have eaten three of your five fruits and veggies for the day. Writing a menu plan before you go to the market will save time and energy, and ensure you get all the fresh foods you need.

It can be hard to exercise if you have an MPD, but you can always start small and increase over time. This is a terrific way to improve your energy levels and circulation while reducing your risk of major complications. If you feel fatigued and don't know where to start, it's helpful to wear a pedometer for a week to see how many steps you take. You can then gradually add ten minutes of walking to your longest daily walk, aiming to increase the number of steps you take over several weeks. Walking 10,000 steps a day will keep you very fit. For lots more information about keeping fit, visit www.cancerresearch.co.uk. □

Know the signs of a DVT

A deep vein thrombosis (DVT) is a blood clot that develops in a deep vein, usually in the lower leg. Deep vein thrombosis can cause pain in the leg and can potentially lead to complications. A DVT usually develops in a deep vein in the leg but can occur elsewhere, such as in the arm. Although air travel is widely thought to increase risk of DVT, the risk increases for long journeys regardless of mode of transport.

In most cases of DVT, the clots are small and do not cause any symptoms. The body is able to break down the clot and there are no long-term effects. Larger clots may partially or totally block the blood flow in the vein and cause symptoms such as:

- Swelling of the calf - this is usually different from the mild ankle swelling that many people get during long haul flights
- Pain in the calf
- Calf pain that is noticeable, or worse when standing or walking

These are not always a sign of a DVT, but if you experience them, you should seek medical advice. □

> *"In most cases of DVT, the clots are small and do not cause any symptoms. The body is able to break down the clot and there are no long-term effects."*

Travel and DVTs—the facts

All long journeys by any mode of transport —be it by plane, car or train—may increase the risk of deep vein thrombosis (DVT). The risk is not as great the media would suggest: in fact we estimate the risk to be one DVT per million passengers on flights over six hours.

The best way to prevent DVT is to keep well hydrated, avoid alcohol, regularly flex your ankles to contract calf muscles, and walk around if possible. It's advisable to wear flight socks for journeys longer than four hours unless they are contraindicated (poor circulation to legs or ulcers due to arterial disease). Most MPD patients do not require additional protection. However, some patients may be advised to take an injection of heparin prior to the flight, especially if they have had recent or multiple thromboses, a clotting event, or are pregnant (< six weeks after delivery), or have recently undergone surgery. Heparin is simple to give, and your haematologist can provide a letter explaining its use for airline security. Talk to your doctor about your travel plans, and have a safe trip! □

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Mayo Clinic & Harvard identify new mutations

Researchers at the Mayo Clinic and Harvard University in the U.S. have identified two additional mutations that may play a role in myeloproliferative disease. The JAK2V617F discovery is exciting news, yet many patients with ET and MF test negative for JAK2. The Mayo/ Harvard study sought to answer questions about patients who do not carry JAK2V617F.

Some evidence suggests that more than one mutation may lead to myeloproliferative disease. The researchers decided to look at the JAK-STAT signalling pathway, to search for additional mutations, and identified two mutations called MPLW515L and MPLW515K. The first occurs in about 5% of patients with MMM or ET; the second in 1% of the same patients. A few patients carried both the MPLW515L and the JAK2V617 mutations, while patients with PV did not carry these 515L and K mutations.

The researchers believe a designer drug in the form of a "small molecule inhibitor" could be used to treat patients suffering from MPDs with the MPLW515L mutation, just as a similar type of inhibitor could help patients with the JAK2 mutation. Drugs like this could be effective in treating and potentially curing the disease.

This new research also suggests that other as yet undiscovered mutations may exist, and research should continue to discover these. □

Get involved!

Buddy Program: MPD-Support can use your help. If you would like to act as a patient-counsellor, please email us at info@mpd-support.co.uk for more information about training to be a patient "buddy."

Fund-raising: Would you like to help raise monies for MPD-Support to fund research for better, more effective medications? If you'd like to run or bike for MPD-Support, please email us: info@mpd-support.co.uk.

Professor Tony Green on JAK2... *(article continues from P2)*

these disorders. The news on the JAK2 mutation may completely alter the way we think about MPDs. Professor Green's team is studying banked patient blood samples to analyze changes in JAK2 positive and negative patients over time. Until 2005, we grouped the myeloproliferative disorders into three distinct diseases: ET, PV and MF. We now know that:

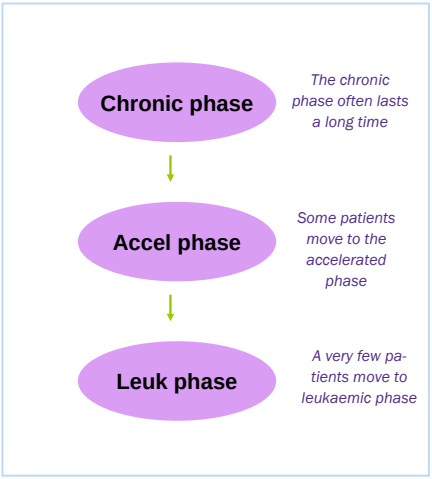
- About 50% of ET patients are JAK2+
- About 50% of ET patients are JAK2-
- 97% of PV patients are JAK2+

Patients with JAK2 positive ET and PV share many disease attributes. Certain JAK2 positive individuals (and men in particular) produce more red blood cells, while others produce more platelets – an individual's sex and genetic background may play a role. Perhaps we should look at these patients as having a JAK2 positive MPD, rather than classifying them as having either ET, PV or MF.

JAK2 negative patients move along a similar continuum, from JAK2 negative ET to MF. We might reclassify these patients as having a JAK2 negative MPD.

Professor Green posits that there may in fact be two separate diseases. The diseases follow similar paths: first, the patient moves through a chronic phase, which can last for a long time. Later, some patients move into an accelerated phase. An unlucky few worsen and move into a leukaemic phase. What we think of today as ET, PV and MF may in fact be phases of an MPD which is either JAK2 positive or negative.

Professor Green believes reclassifying MPDs may give doctors more insight in treating these illnesses. With new understandings of how MPDs work, we'll be able to manage them more effectively. □



Possible disease paths: JAK2 positive and negative MPDs