New treatment against transplantation complications tested

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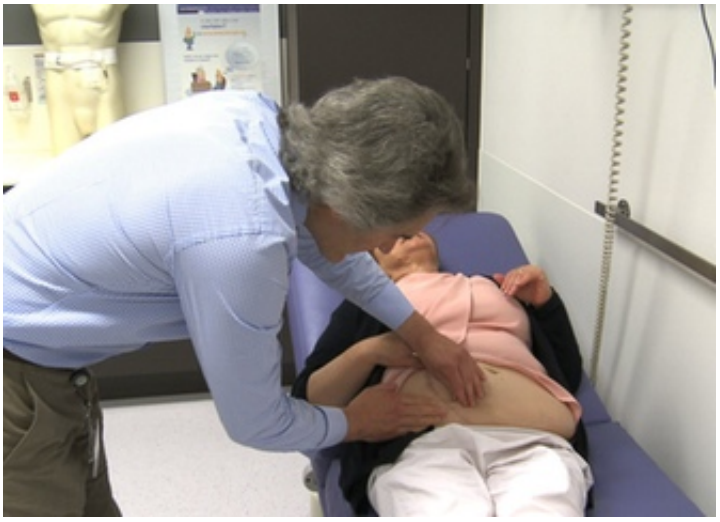

It is not uncommon for kidney transplants to fail. Once transplanted, the kidney must connect back with the blood supply to start working properly and be truly accepted by the body. Delays can cause complications. An example, known as delayed graft function (DGF), is where the new kidney can become inflamed while starved of blood supply. This serious complication affects over half of those who receive kidneys from deceased donors.

Now, a solution may be in sight. A new drug candidate, belonging to the family of monoclonal antibodies, called OPN-305 is capable of

dampening down the body's immune response to a donated kidney. Developed since 2005 by a biopharmaceutical company in Dublin, Ireland, called Opsona Therapeutics, studies have confirmed that it works in animals and is not toxic. An initial clinical trial in healthy humans, referred to as phase I study, has shown it is safe. Now, as part of the EU-funded project MABSOT, the drug will be tested on a number of patients. This will be a proof-of-concept, so-called Phase II, clinical trial.

"There are huge health benefits and economic benefits for people if this candidate actually works. There is nothing approved for DGF, so this would greatly improve the quality of life for people who would ultimately end up on dialysis," says project coordinator Mary Reilly, vice president of Pharmaceutical Development and Operations at Opsona Therapeutics.

Inflammation is caused by the immune response. Proteins called Toll-like receptors recognise invading microbes and sets off the body's defences. But OPN-305 binds this key receptor and stops it from triggering the body's immune system. "The OPN-305 antibody binds to Toll-like receptor 2 (TLR2) and effectively switches off the signal that provokes inflammation," explains Reilly. "The inflammation that it reduces is a major cause of poor kidney function immediately after transplantation," she tells youris.com.

To assist in the development of OPN-305 it was granted orphan drug status. This means the regulator giving it some incentives in recognition of its importance to treat unmet medical needs. Indeed, there are no other treatments for DGF. "This particular compound has the potential to be the first and best in class," says Reilly. "There is nothing else out there for this disease, so it could really transform people's quality of life." However, tests for its effectiveness and safety remain just as stringent as for any drug.

For this trial, OPN-305 will be given to organ recipients on top of the existing standard treatment. Altogether, 50 medical centres in the US and in Europe will be involved in this Phase II trial, with 270 patients opting to be involved. "If Phase II is successful, the next step will be to move to a Phase III clinical study. This is a larger clinical study with a more mixed population," Reilly explains. The Phase III trial is the final hurdle in an approval process that can take 10 years or more alltogether.

One expert believes the project is quite challenging. "In this project they humanised a mouse monoclonal antibody. So they took its mouse amino acids and changed them to be like human amino acids. We call that humanising the antibody and it is quite challenging," comments Dr Pierre Lafaye, head of antibody engineering at the Institut Pasteur, in France.

And there could be unforeseen effects. "It could trigger a secondary effect not observed in vitro or in mice. So sometimes that could be a headache or fever or something like that. At the biological level there are differences between a mouse model and human, so I think this is quite an interesting project. But in clinical development you never know if it is going to reach a successful end," Lafaye tells youis.com.

Lafaye says that monoclonal antibodies have had a major impact in the field of cancer therapy. But not so much in autoimmune diseases. Asked about alternative strategies for organ transplants, he says: "A small chemical compound that is able to interact with TLR-2 could work, but these small compounds usually have a short half-life [which means that they do not necessarily stay long enough in the body to be effective]. Monoclonal antibodies have half-lives of several days." This means they hang around in the body for longer – a half-life is the time it takes for half of a given compound to be broken down.

Another expert believes the approach is promising. "Monoclonal

antibodies have been used in some autoimmune conditions such as rheumatoid arthritis," says Anne Cooke, a professor of immunology at the University of Cambridge, UK. "TNF blockers such as the drug Infliximab and B-cell depleters such as the drug Rituximab have been used in rheumatoid arthritis (RA). TNF blockers have been life-changing, having terrific results in a good proportion of RA patients," she tells youris.com. Asked about advantages of using monoclonal antibodies, she notes "perhaps increased specificity over more generalised immune suppression." This means that antibodies are more preferentially targeted and this should therefore produce fewer side effects.

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