ABSTRACT

Background: The wound healing process is divided into four phases: haemostasis/coagulation, inflammation, proliferation, and wound remodelling. The wound closure needs a perfect control of these phases thus wound management is always a challenge. Numerous factors, like medications, can markedly affect most aspects of the wound healing process.

Aim: We want to focus our attention on the mammalian target of rapamycin (mTOR). Deregulation of the mTOR signalling pathway occurs frequently in human malignancies. The pharmacological inhibition of mTOR with rapamycin and its analogs is used in organ transplantation to prevent rejection and to slow skin carcinogenesis in organ recipients.

Methods: This article reviews the recent literature on the mTOR inhibitors and the potential cellular and/or molecular mechanisms involved in the wound healing process.

Results and conclusions: The mTOR inhibitors can affect all steps of the healing process by decreasing the inflammatory cell number, angiogenesis, and myofibroblast proliferation. The frequent association, among organ recipients treated by mTOR inhibitors, with other immunosuppressive therapies and comorbidities exacerbate the risk of wound healing complications. The complexity of the mTOR pathway is not completely understood but its role in the wound healing process is crucial. The indication for the mTOR therapy has to be discussed carefully for each patient.

MECHANISMS OF ACTION

The mTOR is an important kinase necessary for physiological cellular activities acting by forming two complexes: the mTOR complex 1 and the mTOR complex 2. The result of the activation of complex 1 is the promotion of cell proliferation, the angiogenesis process and protein synthesis. The mTOR complex 2 activity is essential for the transformation and vitality of a number of cancer cell types, but in many normal cells, mTOR complex 2 activity is less essential.

The rapamycin can inhibit the activation of the mTOR complex 1 by binding to an intracellular receptor FKBP12, but how this interaction antagonises the mTOR complex 1 is not well understood.

In that way, rapamycin is able to cause an immunosuppression by inhibiting the signal transduction pathway required for the progression of cytokine-stimulated T-cells from G1 into S phase. In addition, many enzymes along the signalling pathway that are inhibited by the rapamycin play
a role in the development and progression of different cancers and metabolic disorders such as diabetes or atherosclerosis.

The mTOR pathway is upregulated in many other conditions such as in polycystic kidney disease and neurofibromatosis.

The mTOR pathway is a complex network with a variety of positive and negative regulators but all these mechanisms are not completely explained\(^{(6,7,8)}\).

**SIDE EFFECTS**

Despite their attractive pharmacological properties, side effects are associated with mTOR use in 20-40\%\(^{(9)}\) of patients. Some side effects are easily manageable, whereas others lead to discontinuation of the drug. The anaemia, thrombocytopenia, neutropenia, proteinuria, lymphedema and hyperlipidemia are the most reported dose dependent side effects\(^{(10,11)}\).

Cutaneous side effects have also been reported such as wound healing impairment. Such skin side effects have also been reported with the use of anti-vascular endothelial growth factor (VEGF) therapy and could therefore be a limiting factor for their use\(^{(12)}\).

**CUTANEOUS SIDE EFFECTS**

Pruritic follicular papulo-pustular eruption represents a typical side effect occurring early after the initiation of the mTOR inhibitors therapy. This effect is mostly temporary and usually improves within a few weeks\(^{(13)}\).

Pruritus and xerosis are frequently reported by the patients receiving mTOR inhibitors therapy\(^{(13)}\).

Cases of angioedema have been reported but all the patients were simultaneously treated with angiotensin-converting enzyme inhibitors. The resolution of the angioedema was observed after the withdrawal of the angiotensin-converting enzyme inhibitors\(^{(14)}\).

The development of buccal ulcerations and stomatitis are a common and potentially dose limiting toxicity associated with the use of mTOR inhibitors in cancer treatment\(^{(13)}\).

The interactions of the mTOR inhibitors on the healing process are important cutaneous side effects. Wound infections, incisional hernias and wound dehiscence have also been reported\(^{(15)}\).

**WOUND HEALING IMPAIRMENT**

A normal healing process can be divided in four steps: haemostasis and coagulation, inflammation, proliferation and remodelling. A perfect control on each step is necessary for a correct healing\(^{(16)}\).

The mTOR inhibitors can directly interfere with each step of the healing process but more specifically on the inflammation and proliferation stages. They are able to inhibit the angiogenesis process by decreasing the level of the VEGF, they can also decrease the activity of the intraepithelial gd T cells and cause an inhibition of the smooth muscle cells, fibroblast proliferation and matrix deposition. This would decrease the formation of scar tissue and compromise blood flow to the defect.

The crucial role played by the mTOR in the healing process has yet to be examined in detail\(^{(17)}\).

The mTOR inhibitors can also indirectly interfere with the repair process. Their immunosuppressant properties increase the risk of infection. The anaemia, hypoproteinemia and lymphedema secondary to the mTOR inhibitors therapy are also risk factors for healing complication and delayed healing\(^{(18,19)}\).

**MANAGEMENT**

The management of wound healing complications in patients treated by mTOR therapy is difficult. The clinicians have to be aware of the potential healing impairment caused by mTOR therapy.

We have reviewed the recent literature concerning mTOR therapy and its impact on the wound healing process. There is no standardised guideline concerning the management of healing complications. We have found some recommendations; with a level three of evidence based medicine, proposed for the use of the mTOR inhibitors in the transplantation medicine\(^{(20)}\).

We have summarised the important points:

- Before starting the mTOR inhibitors therapy, it is recommended that the risk factors for wound healing complications are checked. Factors like the use of concomitant immunosuppressive therapy, obesity, and smoking are modifiable risk factors. The patient’s age, sex and ethnic origin are non-modifiable risk factors. Any modifiable risk factor should be addressed. If a non-modifiable risk factor is identified, a risk–benefit analysis should be performed and, if appropriate, an alternative treatment to mTOR inhibitors should be considered.

- Some clinicians are narrowing or even discontinuing the use of steroids in the early post-transplant period. It is also recommended to avoid the use of the mTOR inhibitors during the first week post-transplantation.

- The impaired healing is a dose-dependent side effect. A cumulative rapamycin dose of more than 35 mg during the first four days post-transplantation is a risk factor for impaired healing. It is highly recom-
Conclusions: The development of the mTOR inhibitors is an interesting therapeutic option thanks to their different immunosuppressive properties. They are mainly used in transplant medicine and oncology. The involvement of the mTOR pathway in many disorders such as neurofibrmatosis and polycystic kidney disease has enlarged their indications.

One of the major benefits of rapamycin is that it is an immunosuppressant that inhibits carcinogenesis, whereas other immunosuppressants are thought to increase carcinogenesis like the calcineurin inhibitors. The effect of the mTOR inhibitors on carcinoma is likely inhibition of angiogenesis and an associated decrease in vascular endothelial growth factor.

Unfortunately the use of the mTOR inhibitors is associated with many side-effects. Some of these are manageable, whereas others could be limiting factors for mTOR use.

This article gives you a general overview of the effects of mTOR inhibitor therapy. Our article sought to point out their important impact on the skin healing process.

The management of this side effect is based on a number of recommendations with a level three of evidence based medicine. Control of the risk factors for wound complication is a crucial step before starting such therapy. The complexity of the mTOR pathway is not completely understood but its role in the wound healing process is crucial. The indication for the mTOR therapy has to be fully discussed and the risk-benefits balance must be considered carefully for each patient.

It would also be interesting in the future to develop guidelines regarding their use in the oncology field.

References:

9. Rostaing L et al. mTOR inhibitor/proliferation signal inhibitors: entering or leaving the field. J nephrol. 2010:23 (02) : 133-142.