international wound journal

International Wound Journal ISSN 1742-4801

ORIGINAL ARTICLE

Effects of immunosuppressive therapy on wound healing

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Key words
Immunosuppressive agents; Wound healing

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Bootun R. Effects of immunosuppressive therapy on wound healing. Int Wound J 2013; 10:98–104

Abstract

Immunosuppressive therapy is increasingly being used in clinical practice and has been shown to affect wound healing to varying degrees. This article looks at the effects of the newer immunosuppressive agents on wound healing. It is shown that wound healing is impaired via different mechanisms. Some of the animal and human studies are reviewed in more detail. It is shown that some of the newer agents affect wound healing to such an extent that reduction or avoidance of these drugs until complete wound healing is achieved is advocated. More research is required for these newer agents to determine the most appropriate time to introduce them.

Introduction

Wound healing entails a complex and well-coordinated series of events (1), involving a wide variety of cells, hormones, cytokines, proteases and growth factors (2). It is recognised to comprise of different phases, namely, haemostasis, inflammation, proliferation and repair and remodelling (2). Immunosuppressive agents, used in conditions such as organ transplant and inflammatory bowel disease, have been shown to impair this wound healing process (3). This work will look at the mechanism of action of some of the commonly used immunosuppressive drugs as well as studies which have been carried out in animal and humans.

Wound healing

Wound healing is a complex process involving four overlapping processes, namely, haemostasis, inflammation, proliferation and remodelling (1,4). Tissue injury leads to extravasation of blood into the wound and eventual clot formation. The clot that forms is made up of collagen, platelets, thrombin and fibronectin, and these factors release cytokines and growth factors that initiate the inflammatory response (5). The inflammatory phase involves the chemoattraction of neutrophils and monocytes to the site of injury (6). As inflammation progresses, the number of neutrophils decline and macrophages (tissue-derived monocytes) predominate (4). Neutrophils destroy bacteria by releasing caustic proteolytic enzymes (5). Activated macrophages, along with clearing the wound of dead neutrophils, bacteria and debris, also release a number of cytokines which are essential for angiogenesis [e.g. vascular endothelial growth factor (VEGF)] and fibroplasia [e.g. transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF)] (5). The proliferative phase ensues with fibroblast migration, deposition of extracellular matrix and formation of granulation tissue (1). Fibroblasts synthesise collagens, which are the most abundant family of proteins in the body (1). Twenty-one different types of collagen have been identified so far (5). The collagen molecule is characterised by the repeating sequence Gly-X-Y, with X often being proline and Y being hydroxyproline (5). The molecule undergoes eight post-translational steps before it is secreted as procollagen, a triple helix (5). The ends of the molecule are then cleaved, decreasing the solubility of collagen (5). The next step is remodelling and scar formation. The synthesis and remodelling of the extracellular matrix is initiated concurrently with the development of granulation tissue and continues over prolonged periods (1). Wound contraction follows with the interactions between fibroblasts and the surrounding extracellular matrix and is influenced by a number of cytokines including TGF-β, PDGF and basic fibroblast growth factor (1). Scar formation eventually results, but with the wound not achieving the same strength as the original unwounded skin (1).

Key Messages

- wound healing entails a complex and well coordinated series of events namely, haemostasis,inflammation, proliferation and remodelling
- immunosuppressive agents, used in conditions such as organ transplant and inflammatory bowel disease, have been shown to impair this wound healing process

- this work will look at the mechanism of action of some of the commonly used immunosuppressive drugs as well as studies which have been carried out in animal and humans
- forty eight Wistar rats were divided into groups of 4 per cage, then randomised into three groups receiving one daily dose of placebo, low dose AZA and high-dose AZA, respectively
- colonic anastomosis was performed and the animals were sacrificed 3 days postoperatively
- the breaking strength of the anastomosis was then determined
- there was no significant differences in anastomotic breaking strength between the three groups
- the strengths of this study are the inclusion of a control group and having a low-dose and high-dose treatment group to ascertain the effect of different doses on healing
- in addition, the method for testing breaking strength is well described and has been shown to be superior to other methods for measuring anastomotic healing
- no blinding was involved, so that the investigator performing the colonic anastomosis could potentially be aware of which group the rats came from
- immunosuppressive agents have been used in different types of organ transplants to reduce rejection rates
- however, through their interactions with some of the inflammatory mediators, they influence the wound-healing process
- reduction of the dose used or even avoidance of the drugs until complete wound healing has been achieved has been advocated, especially, for the newer immunosuppressants (e.g. everolimus)
- at this time, more research into the possible effects of immunosuppressive drugs, especially, the newer mTOR inhibitors, would be beneficial to clearly identify when they should be introduced

Several inflammatory mediators involved in the wound-healing process are affected by immunosuppressants. Interleukin (IL)-2 activates macrophages, T cells, natural killer cells and lymphokine-activated killer cells as well as stimulates the differentiation of activated B cells and proliferation of activated B and T cells (5). IL-4 stimulates fibroblast proliferation early in the wound-healing process and, later on, downregulates cytokine expression (5). Interferon-γ (IFN-γ) and tumour necrosis factor-α (TNF-α) are both leucocyte chemoattractants, while IFN-γ and granulocyte-macrophage colony-stimulating factors (GM-CSF) are leucocyte activators (5).

Mode of action of immunosupressant drugs

Cyclosporine A (CsA) is a cyclic peptide of fungal origin that inhibits T-cell response (7). It binds to cellular proteins called cyclophilins intracellularly to create the active complex CsA–cyclophilin (8). This complex subsequently inhibitis calcineurin, which is a serine threonine phosphatase necessary to activate transcription factors like nuclear factor of activated T cells (NFAT) (8). When calcineurin is inhibited, cytokine genes (IL-2, IFN-γ, GM-CSF, TNF-α and IL-4) cannot be transcribed (8). This cascade of events ultimately results in inhibition of T-cell production and differentiation (7).

Tacrolimus (FK506) is a product of the fungus *Streptomyces tsukubaenis* (7). Although a macrolide like cyclosporine, it differs in its chemical structure and cytosolic binding site (7) and appears to be 10–100-fold more potent than CsA (9). Indeed, tacrolimus binds to proteins termed FK506-binding proteins (FKBP) instead (8). The tacrolimus–FKBP complex binds and inhibits the activity of calcineurin in a mechanism similar to the CsA–cyclophilin complex (8).

The inhibition of T-cell proliferation brought about by either CsA or tacrolimus can be partially reversed by the addition of exogenous IL-2 to in vitro culture, suggesting that the block in T-cell function is proximal to this step (9).

Azathioprine (AZA) is the 1-methyl-4-nitro-5-imidazolyl derivative of 6-mercaptopurine (10). AZA and its metabolites suppress intracellular inosinic acid synthesis, which interferes with intracellular purine synthesis (11). This, in turn, leads to a reduction in the number of circulating B and T lymphocytes and results in reduced immunoglobulin production and decreases IL-2 secretion (11).

Mycophenolate mofetil (MMF) is an ester of an old drug, mycophenolic acid (MPA) (12). MPA was originally obtained from a *Penicillium* species and had antifungal activity. MPA eventually turned out not to be as useful as an antibiotic, but there has been interest in this drug as an immunosuppressant (12). It is an antimetabolite agent that interrupts purine metabolism in T and B lymphocytes (7). Purine biosynthesis occurs via two distinct pathways (8). In resting T and B lymphocytes, the de novo pathway operates by converting 5-phosphoribosyl-1-pyrophosphatge to inosine monophosphate (IMP) (8). This is changed to guanosine monophosphate (GMP) by the rate-limiting enzyme inosine monophosphate dehydrogenase (IMPDH) in the salvage pathway. Guanosine triphosphate is subsequently produced and becomes involved in DNA synthesis. MPA is a potent, selective, reversible non competitive inhibitor of IMPDH. Inhibiting IMP depletes intracellular GMP pools, while leaving adenosine triphospate pools unaffected. MPA inhibits the generation of cytotoxic T cells and the rejection of allogeneic cells. It has been shown to suppress the formation of antibodies against alloantigens in a chronic rejection model and to abolish the formation of antibodies against xenogeneic cells (8).

Sirolimus (SLR) (previously called rapamycin) is a microbial product isolated from the actinomycete *Streptomyces hygroscopicus* (13). It was initially isolated from a soil sample harvested on Easter Island (Rapa Nui) (8). Akin to tacrolimus, it binds to FKBP (FKBP-12) (10). However, these two immunosuppressant drugs affect different and distinctive sites in the signal transduction pathway (10). The drug–receptor complex blocks the activity of a cytoplasmic serine–threonine kinase known as mammalian target of rapamycin (mTOR) (14). The latter is the downstream effector of the phosphatidylinositol-3 kinase-Akt signalling pathway and is a crucial checkpoint in several cell functions, including cell growth and proliferation (14). Other activators of mTOR include IL-2, IL-15, oncogenic proteins and VEGF.

Inhibition of this essential cytoplasmic kinase by SLR in T cells impedes their clonal expansion in response to alloantigen and represents the basis of the immunosuppressive action of the drug (14).

Everolimus is similar to SLR and its mechanism of action seems to be through the blocking of the cytokine-mediated proliferation of T and B cells by interrupting second messenger signalling (7). Everolimus binds to FKBP-12 and creates an active moiety that effectively blocks the mTOR and thereby arrests the cell cycle of lymphocytes and vascular smooth muscle cells in the G_1 phase (15). In addition, it exerts immunosuppressive effects via inhibition of IL-2 and IL-15-mediated T- and B-cell proliferation (15).

Method

The existing literature was searched using the Web of Knowledge database (Thomson-Reuters). The words 'immunosuppresive agent' and 'wound healing' were searched separately and the references were cross-referenced. In total, 378 references were obtained. Additional searches were carried out with the words 'wound healing' cross-referenced with the immunosuppressive therapies included in this review. These were cyclosporine, AZA, MMF, tacrolimus, rapamycin, SLR and everolimus. Only articles which were looking at the effects of the above immnunosuppressants on wound healing were selected. Articles looking at the use of steroids in immunosuppression were excluded as it would have been too broad an area to cover within this review.

Effects of immunosuppresive therapy on wound healing

Animal studies

AZA and its metabolites suppress intracellular inosinic acid synthesis, which interferes with intracellular purine synthesis leading to a reduction in the circulating B and T lymphocytes (11). This also results in reduced immunoglobulin production and decreased IL-2 secretion. Stolzenburg et al. studied the effect of AZA on anastomotic healing in rats. Forty-eight Wistar rats were divided into groups of 4 per cage, then randomised into three groups receiving one daily dose of placebo, low-dose AZA and high-dose AZA, respectively. Colonic anastomosis was performed and the animals were sacrificed 3 days postoperatively. The breaking strength of the anastomosis was then determined. There was no significant differences in anastomotic breaking strength between the three groups (16). The strengths of this study are the inclusion of a control group and having a low-dose and high-dose treatment group to ascertain the effect of different doses on healing. In addition, the method for testing breaking strength is well described and has been shown to be superior to other methods for measuring anastomotic healing (16). No blinding was involved, so that the investigator performing the colonic anastomosis could potentially be aware of which group the rats came from.

T lymphocytes play an important role in wound healing, especially in the inflammatory phase (17). Baum and Arpey also noted that depletion of CD4+ T cells (helper T cells) resulted in decreased wound strength. CsA appears to inhibit helper T cells while sparing suppressor T cells, thereby augmenting overall suppressor cell function (18). Fishel et al. undertook a prospective case–control study looking at the effect of CsA, a then new immunosuppressive agent, on wound healing in Sprague-Dawley rats. The rats were kept in a controlled environment and were allowed to acclimatise themselves to the laboratory conditions prior to the start of the experiments. The backs of the animals were shaved and an incision was made down to the level of the panniculus carnosus. At the upper poles of the wound, subcutaneous pockets were created into which sterile preweighed saline-moistened polyvinyl alcohol sponges were inserted. CsA dissolved in olive oil was given to the study group by gavage, while the control group received an equivalent volume of olive oil. The rats were sacrificed on the tenth post-wounding day and the pelt containing the healing scar was excised. Thymus, spleen and adrenal glands were removed and weighed. Lymphocytes from each thymus gland were collected. Wound strips from the CsA animals weighed less than controls ($0{\cdot}90 \pm 0{\cdot}01$ g versus $0{\cdot}96 \pm 0{\cdot}02$ g, $P < 0{\cdot}01$). Wounds from CsA-treated animals had decreased fresh (282 ± 19 g versus 380 ± 27 g, $P < 0{\cdot}01$) and formalin-fixed (1111 ± 74 g versus 1419 ± 57 g, $P < 0{\cdot}01$) breaking strengths. The impairment in wound breaking strength was paralleled by a significant decreased in the hydroxyproline content of the sponge granulomas in the CsA group (1276 ± 70 versus 1598 ± 67 μg/100 mg dry sponge weight, $P < 0{\cdot}01$). The data, therefore, showed that CsA, at an immunosuppressive concentration, markedly impairs wound healing. The CsA-treated animals had weaker wounds, as reflected in the fresh breaking strengths, and synthesise less collagen, as shown by the hydroxyproline content of the sponge granuloma. As the CsA-treated animals have less collagen available for cross-linking, the formalin-fixed breaking strengths are also decreased. This was a well-conducted study with objective evidence of the effect of CsA on wound healing. This study is, however, conducted in rats, and, therefore, it not possible to ascertain whether similar effects would be seen in humans.

Hasegawa et al. looked at the effect of tacrolimus on tissue repair after full-thickness wounding on rabbit ear. Four full-thickness wounds were made on the inner side of each ear. The wounds were covered with sterile transparent dressings and TGF-β and/or tacrolimus applied to each ear. The rabbits were sacrificed on day 7 post-wounding and, then, the amount of granulation tissue and the degree of the reepithelialisation were assessed. TGF-β enhanced granulation formation and reepithelialisation in the rabbit ear, both of which were blocked by the addition of tacrolimus (19).

MMF is another immunosuppressive agent that blocks the de novo synthesis of purine nucleotides by inhibiting the enzymatic activity of IMPDH, which also results in the impaired proliferation of T and B lymphocytes and macrophages (20). Zeeh et al. looked into the effect of MMF on the healing of left-sided colon anastomosis in Sprague-Dawley rats. The animals were divided into two groups ($n = 21$ each) (21). MMF or vehicle was administered intraperitoneally once daily

until euthanisation (seven animals per group: 2, 4 and 6 days after surgery). After oral application, the bioavailability of MMF in humans is nearly 100% and pharmacokinetic measures are similar in humans and rats (21). The anastomoses were hand sutured and the bursting pressure was evaluated. Three of the animals died during the operative procedure. More extensive inflammatory activity was noted in the MMF-treated animals. Indeed, the inflammatory score on day 6 was 2·67 ± 0·21 and 1·67 ± 0·33 ($P < 0·05$) in MMF- and vehicle-treated animals, respectively. The bursting pressures (mmHg) were significantly lower in MMF-treated animals when compared with controls. This study, therefore, shows that MMF inhibits injury-induced reparative proliferation of colonic mucosa cells (21). The strengths of this study include the fact that blinding occurred when the rats were having their surgeries performed so that the investigator performing the procedure was unaware of what group the rat was from. Bursting pressures were also evaluated with investigators blinded to the test animals. Limitations include the fact that this study was conducted in rats and it is not possible to accurately determine whether similar effects would be observed in humans.

Gaber et al. looked into the changes in abdominal wounds following treatment with SLR and steroids in a rat model. Sprague-Dawley rats were randomised in groups of 18 each to either surgery alone (sham control), surgery plus hydrocortisone alone (steroid control) or surgery plus postoperative rapamycin at one of five different regimens (with or without steroids) (22). The wounds in the control animals had gradual increase in tensile strength during the 15-day observation. However, high and loading doses of SLR caused reduction in wound strength until day 10, but the wounds' tensile strength became equivalent to control by day 15. High dose and loading doses delayed healing for 10–15 days. The authors concluded that the addition of steroids had a synergistic effect on delayed wound healing, particularly in animals receiving high doses of SLR, which showed prolonged wound weakness. This study was well designed with different regimens being used to evaluate the effect of different concentrations of drugs on wound healing. The researchers undertaking biomechanical analysis of wound strength in the tissue samples were blinded as to the treatment received by the rats, thus minimising observer bias. However, the experiment was carried out in rats, which are not perfect representation of humans.

In 2005, Kahn et al. investigated the effect of rapamycin on the healing of ureteric anastomosis and wound healing. Twelve large White/Landrace pigs underwent a midline laparotomy and their ureters were divided, then reanastomosed (23). The animals were randomised to receive either rapamycin or placebo. The results showed that the tensile strength of the ureter in the rapamycin-treated animals was lower than in the control animals (221 ± 24 g versus 261 ± 16 g, $P > 0·05$). The hydroxyproline levels were also decreased compared with the control animals (12·8 ± 2·7 μg/ml versus 22·4 ± 5·3 μg/ml, $P > 0·05$). The tensile strength of the fascia in the animals in the rapamycin group was 417 ± 81 g compared with 444 ± 54 g in the placebo group. This study had clear aims, and measured both tensile strength and hydroxyproline in three different tissue types. The small number of animals used accounts for the differences observed not being statistically significant. An improvement on this study could be to have a larger sample size and maybe having different doses of rapamycin given.

van der Vliet et al. looked at the effects of increasing doses of everolimus on the anastomotic healing in rat intestine. One hundred and four male Wistar rats were randomly divided into four groups of 26 animals each. Three groups received everolimus at different dosages daily, starting 4 hours before the operation until killing. The control (C) group received daily saline. All rats were operated on day 0 and half were killed at days 3 and 7 each. Ten animals from each groups had mechanical and biochemical analysis, while three were used for histological tests. The results showed that the animals receiving the highest dose of the drug had a larger percentage weight loss from day 4 onward ($P < 0·001$) (24). Anastomotic breaking strength at day 7 was significantly reduced in a seemingly dose-dependent manner in almost all experimental groups (24). Thus, everolimus, another mTOR inhibitor, is shown to adversely affect wound healing in rat intestine.

Human studies

Tacrolimus and cyclosporine have been shown to suppress T-cell activation through the inhibition of calcineurin and the calcineurin-dependent transcription factors NFAT (25). On the other hand, SLR, an mTOR inhibitor, has been suggested to prevent fibroblast proliferation and inhibits angiogenesis (26). It has been shown to reduce the expression of VEGF and nitric oxide, and inhibits smooth muscle cells and fibroblast proliferation and matrix deposition (27). In 2004, Dean and his colleagues looked into the wound-healing complications following kidney transplantation. They conducted a prospective, randomised comparison of the effects of SLR and tacrolimus. One hundred and twenty-five patients were enrolled, with 64 assigned to the SLR group and 61 to the tacrolimus group. Two of the patients from the tacrolimus group were subsequently excluded because they did not receive the study medication because of early graft thrombosis. A further six patients from the same group died later on. Thirty-five patients (28%) developed wound complications [5 (8%) from the tacrolimus group and 30 (47%) from the SLR group]. This difference was statistically significant. Some of the patients from the SLR group required readmission and reoperation to deal with the wound complications. It has been suggested that given the high incidence of wound complications, it might be more cost effective to use lower or even avoiding the use of SLR until the wound has healed (14,26). The strengths of this study were that it was prospective and that the patients were randomised at the start. The number of patients recruited seemed to have been enough to have statistically significant results, but the inclusion of more patients would probably improve the strength of this study.

Rapamycin and everolimus are other members of the class of drug known as mTOR inhibitors. These drugs have strong antimitotic activity, preventing the proliferation of lymphocytes despite IL-2 stimulation (28). They also slow the progression of neointimal hyperplasia, thus causing

impairment of wound healing. Dean et al. had suggested the use of delayed mTOR inhibitors to allow wound healing prior to starting the antirejection therapy. In 2009, Albano et al. conducted a prospective, multicentre, open-label study looking at the incidence of delayed graft function and wound-healing complications after deceased-donor kidney transplantation. The authors studied the effect of everolimus on kidney transplant recipients. The recipients were randomised to receive everolimus therapy either on day 1 post-transplant (immediate everolimus – IE group) or from 5 weeks post-transplant (delayed everolimus, DE group) (29). The patients were followed for 3 months initially, although the total duration of this study was going to be 12 months. One hundred and thirty-nine patients were randomised (65 patients in the IE group), but at the 3-month point only 78·5% of the IE group were still on the study medication compared with 71·6% of the DE group. This study was analysed using an intention-to-treat analysis and wound-healing complications related to the initial surgery was one of the primary endpoints. At 3 months, there were 36·9% incidence of wound-healing complications compared with 37·8% in the DE group. However, this was not statistically significant. This study was well designed and followed a preagreed protocol. Ethics approval had been received prior to the start of the trial. The wound-healing complications that were being looked for had been clearly described and patients were reviewed at 4 weeks and 3 months. There was, nonetheless, no control group in this study, making direct comparison with patients not on immunosuppressive agents complicated. It was a multicentre study, but information about wound-healing complications at the individual centres was not made available. More than 21% of the IE group had been changed to a different medication by the 3-month period compared with about 29% in the DE group. The reasons for discontinuing treatment have been given, but these still represent a rather large number of patients who stopped the study medication. In addition, this study was supported by Novartis Pharma, a pharmaceutical company and a number of the study investigators have received grants or are members of the group.

Burgos et al. studies the surgical complications following kidney transplant procedures while using new immunosuppressive regimens. Three-hundred and fifty-nine cadaveric transplants were retrospectively evaluated for the incidence of various surgical complications which included impaired wound healing. This study found that the incidence of wound-healing complications in the transplant patients was not significant (30). This study included the use of different immunosuppressive regimens, but unfortunately, some of the regimens were not as frequently used compared with others. A direct comparison was made between cyclosporine and tacrolimus, and there was a statistically significant difference noted in the rate of collection formation (12% versus 3·8%; $P < 0·05$) and bleeding (11·5% versus 3%; $P = 0·02$), respectively. The mTOR inhibitors were being compared against other regimens and it was found that incidence of lymphocoeles was higher in regimens with mTOR inhibitors compared with those without (16% versus 3·7%: $P = 0·12$) (30). It is also to be noted that the definition of wound-healing complications has not been properly described and that the overall incidence of wound-healing complications in the transplant patients has not been reported, so that it is difficult to judge the real effect of immunosuppressive therapy on wound healing.

In 2003, Valente et al. compared the effects of SLR and MMF on surgical complications and wound healing in adult kidney transplantation. A retrospective sample of 158 patients was included in this study, with 84 receiving MMF (group 1) and 74 receiving SLR (group 2) (31). Overall, 42 wound complications were observed in 34 patients (21·5%). The incidence of wound complications was 2·4% (2 patients) for group 1 and 43·2% (32 patients) for group 2 ($P < 0·0001$). This was a well-designed study, with clear information about the dosing regimens, and statistical methods used. The demographics data were appropriately tabled, as were the data on wound complications. However, there was no randomisation in this study. African American patients were specifically chosen to receive SLR therapy by the institution's study protocol. Thus, in the end, 89% of the MMF group was Caucasians and 88% of the SLR group was African American. This seems quite unusual, especially since at the time, SLR was a recently introduced drug, thus putting a greater number of individuals from this particular racial group at risk from potentially unrecognised adverse effects.

Brewer et al. investigated the effects of SLR on wound healing in dermatologic surgery. It was a retrospective study conducted at the Mayo Clinic (MN) looking at wound healing in patients who had undergone dermatologic treatment at the institution following an organ transplant procedure. The study group comprised of 26 patients who were on SLR at the time, whereas the control group included 37 transplant patients who were on other immunosuppressive agents. The incidence of wound dehiscence was higher in the SLR group (7·7%) than in the control group (0%, $P = 0·17$) (32). In the SLR group, 19·2% of patients reportedly believed that the wound was slow to heal compared with 5·4% in the control group ($P = 0·11$). The strong points of this study are that the dermatologic procedures undertaken are clearly portrayed and the different types of wound complications are clearly displayed. However, this study was retrospective and further information was gathered by telephone interviews. There is, therefore, the possibility of patients not recalling exactly what happened to their wounds and how fast they healed. The small number of patients recruited also reduces the strength of this study. A prospective study with a larger number of patients would be able to give us a clearer idea about the effect of SLR on wound healing.

On the other hand, Grim et al. investigated the risk factors for wound-healing complications in SLR-treated renal transplant recipients. Kidney transplant recipients received different regimens of different immunosuppressive agents. Of 300 patients, 44 (15%) received SLR within the first 6 weeks. Fourteen (31·8%) SLR patients developed wound complications, while the rate of complications in the tacrolimus group was 14·3% ($P = 0·163$) (33). This study had clear tables to illustrate data gathered and included a good literature review about studies previously carried out to look into the effect of SLR. However, this study included only a relatively small number of patients and there was retrospective, with no randomisation at the start.

Summary of studies looking at the effect of immunosuppressive therapy on wound healing

Author(s)	Drug(s) under investigation	Type of study	Type of wound examined	Result
Dean et al. (26)	Tacrolimus, SLR	Prospective, randomised	Abdominal wounds	8% of tacrolimus group and 47% of SLR group developed wound complications.
Albano et al. (29)	Everolimus	Prospective, multicentre, open label	Abdominal wounds	No difference in starting everolimus immediately compared with delaying start.
Burgos et al. (30)	Cyclosporine, tacrolimus, MMF, SLR, everolimus, prednisolone (in different combinations)	Retrospective	Abdominal wounds	Tacrolimus less likely to cause collections or bleeding ($P < 0{\cdot}05$ and $P = 0{\cdot}02$, respectively). Lymphocoeles more common in mammalian target of rapamycin-inhibitor regimens ($P = 0{\cdot}012$).
Valente et al. (31)	MMF, SLR	Retrospective	Abdominal wounds	Incidence of wound complications 2·4% (MMF group) compared with 43·2% (SLR group) ($P < 0{\cdot}0001$).
Brewer et al. (32)	SLR	Retrospective	Dermatologic wounds	Wound dehiscence: 7·7% in SLR compared with 0% in control ($P = 0{\cdot}17$). More patients in the SLR group believed their wounds took longer to heal (19·2% versus 5·4%; $P = 0{\cdot}11$).
Grim et al. (33)	SLR, MMF, steroid and tacrolimus (in different regimens)	Retrospective	Abdominal wounds	31·8% in the SLR group developed wound complications compared with 14·3% in the tacrolimus group ($P = 0{\cdot}163$).

MMF, mycophenolate mofetil; SLR, sirolimus.

Conclusion

Immunosuppressive agents have been used in different types of organ transplants to reduce rejection rates. However, through their interactions with some of the inflammatory mediators, they influence the wound-healing process. Reduction of the dose used or even avoidance of the drugs until complete wound healing has been achieved has been advocated, especially, for the newer immunosuppressants (e.g. everolimus). At this time, more research into the possible effects of immunosuppressive drugs, especially, the newer mTOR inhibitors, would be beneficial to clearly identify when they should be introduced.

Acknowledgement

This work was submitted as an assignment for the MSc in Wound Healing and Tissue Repair (Cardiff University, UK)

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