

Examining the association of immunosuppressants and wound healing: a narrative review

ABSTRACT

Objective A review of recent literature to provide clinicians with an understanding of how different classes of immunosuppressants affect wound healing.

Data sources A literature search was conducted in PubMed, Google Scholar, and the University of Calgary Health Sciences Library.

Study Selection Studies chosen for inclusion were screened initially based on title using key words including “immunosuppressive medication, wound healing, and immunosuppression.” If the title and/or abstract contained these key words and addressed wound healing related to immunosuppressant medications and had been published after 2000, they were included in the review. When human data was not available for an immunosuppressant (class), animal studies were included.

Data Extraction Selected papers underwent full text review and summarisation.

Data Synthesis Data were synthesised in a descriptive manner. Corticosteroids and mechanistic target of rapamycin (mTOR) inhibitors most consistently demonstrate detrimental effects on wound healing. For other classes of immunosuppressants, evidence is limited with varying effects on wound healing described.

Conclusions Larger high-quality studies are required to better understand the effects of immunosuppressants particularly with development of new classes of these drugs on wound healing in order to identify those at highest risk of impairing wound healing.

Keywords Calcineurin inhibitors, glucocorticoids, immunosuppressants, monoclonal antibodies, mTOR inhibitors, wound healing

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INTRODUCTION

Immunosuppressants are medications with a variety of indications including in solid organ and hematopoietic transplants along with autoimmune diseases. They function by

suppressing the activity of various components of the adaptive immune system thus diminishing the cascade of inflammatory response to normal host tissue or modulating the natural rejection response to transplanted materials.¹ The main classes of immunosuppressants are corticosteroids/glucocorticoids,^{2,3} calcineurin inhibitors,^{2,4,5} mechanistic target of rapamycin (mTOR) inhibitors,^{2,4} polyclonal antibodies,^{2,4} monoclonal antibodies,^{2,4} and antiproliferative agents.² For the purpose of this review, wounds are defined as an opening in the skin as a result of surgery, trauma, or disease that is susceptible to infection.

The immune system plays an important role in the prevention of infection but also the healing process of wounds, with the inflammatory effects leading to cellular proliferation and secretion of important intra and extracellular components.⁶ With immunosuppressants, the immune system is modulated, thus potentially affecting a wound’s healing time and

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susceptibility to infection.⁷ With a growing number of patients on immunosuppressing medications, particularly post-surgical transplant patients, the effect of immunosuppressants on wound healing is an important issue to be considered. This review article aims to provide clinicians with an understanding of how different classes of immunosuppressants affect wound healing.

MATERIALS/METHODS

A literature search between 2000 through 2021 was conducted using the generic names of a number of commonly used immunosuppressants (glucocorticoids/corticosteroids, mTOR inhibitors, methotrexate, monoclonal antibodies, polyclonal antibodies, calcineurin inhibitors, mycophenolate, azathioprine) as well as the terms “wound healing” and “immunosuppression”. The primary database searched was PubMed. This was supplemented by Google Scholar and the University of Calgary Health Science Library database. When possible, the search was in the following format “immunosuppressant name [MeSH Terms] AND “wound healing [MeSH Terms].” If the immunosuppressant name was not available as a MeSH term, then the term was searched with no restriction applied. Article titles were then screened for relevance to the review based on whether wound healing was described in relation to the immunosuppressive medication/class. The abstract was screened similarly and included in the review accordingly. If the article compared various immunosuppressants, discussed their effects on wound healing, measured wound healing or deleterious effects on wounds it was considered relevant. If search terms did not identify human subject studies, then studies that used animals to evaluate immunosuppressive effects on wound healing were included. When no data was available from 2000 onwards, a historic search was conducted for the relevant immunosuppressive medications.

All included studies were summarised descriptively including immunosuppressive mechanism of action, study subjects, and evidence of effects on wound healing.

RESULTS

The studies screened relevant to this review were used to inform the various categories outlined below. A total of 200 article titles and abstracts were initially screened and 61 articles were included for review. Summary tables highlighting the results of clinical and animal studies are summarised in Table 1. The specific indications for various immunosuppressants including their possible impacts on wounds are outlined in Table 2.

Calcineurin Inhibitors

Calcineurin inhibitors (CNI) are used as immunosuppressants for a variety of different autoimmune diseases, organ transplants, dermatological conditions, and in chronic wounds.⁸ There are three main types of CNI's: cyclosporine (systemic), tacrolimus (systemic and topical), pimecrolimus (topical).⁹ CNI's work by binding to part of the calcineurin molecule found in

human cells, thus stopping the release of certain cytokines that are responsible for activating T cells.⁸ Therefore, CNI's disable one of the main arms of the body's adaptive immune response.

Systemic

There are a lack of studies directly focusing on the effects of CNI's on wound healing in humans; however, many basic science studies on animals have been performed. Two such studies using rats compared the effect of various doses of systemic tacrolimus versus a control, testing the breaking strengths of the wounds created through surgery. One of the rat studies concluded that tacrolimus does not affect wound healing¹⁰ while the other study concluded that tacrolimus is detrimental to wound healing.¹¹ At the same time, case reports using systemic tacrolimus as a treatment for ulcers in a person with lichen planus and pyoderma gangrenosum demonstrated treatment success with this therapy.¹²

No recent human studies were found regarding the effect of cyclosporine and wound healing. Two other studies using rats also yielded contradictory results. These rat studies focused on the effects of cyclosporine on different markers in the body that signify effective wound healing. One study comparing cyclosporine to methylprednisone demonstrated that cyclosporine had no suppressive effect on the various inflammatory and biochemical markers compared to the glucocorticoid therapy¹³ whereas the other study showed that cyclosporine had a negative effect on the markers.¹⁴ In a different study, after receiving a lung transplant, dogs were assigned to a specific immunosuppressant drug or no immunosuppressant drug and, similar to control, Cyclosporine A was shown to have no significant effect on the healing of the surgical wound as measured by breaking strength in comparison to glucocorticoid and azathioprine immunosuppression.¹⁵ Overall, the literature on systemic calcineurin inhibitors and wound healing is dated with a heterogeneity of comparators and mixed results on wound healing.

Topical

Calcineurin inhibitors (tacrolimus and pimecrolimus) are used as topical ointments most commonly for dermatological conditions such as atopic dermatitis but also for chronic dermatologic conditions such as pyoderma gangrenosum.¹⁶⁻¹⁸ Some case studies have shown tacrolimus effective at healing complex leg ulcers in the context of venous insufficiency or necrobiosis lipoidica, when regular treatment strategies have been ineffective.^{19,20} Furthermore, a rat-based study with acute cutaneous injury demonstrated that wounds treated with topical tacrolimus healed equally as quickly as the control (petrolatum).²¹

Monoclonal Antibodies:

A variety of different monoclonal antibodies (mAb) therapies exist with indications in transplants and autoimmune disorders such as rheumatoid arthritis and psoriasis.²² In general, mAb work by binding to different receptors and antigens to inhibit the effect of cytokines and other signal pathways that

Table 1. Studies Comparing the Effects of Different Immunosuppressants on Wounds

Drug 1	Drug 2	Drug 3	Purpose of Drug	Outcome	Conclusion
Cyclosporine 4-400 mg/kg/day ⁴⁸	Prednisolone 0.75 -75 mg/kg/day to		Treat Pyoderma gangrenosum	Speed of healing (cm ² /day)	No measurable difference between drugs
Systemic Tacrolimus 3 mg twice daily ³⁵	Sirolimus 10 mg daily x 2 days then 5 mg daily		Immunosuppressant after kidney transplantation	Dehiscence, fluid collection, infection, or cellulitis	Wound complications were higher with sirolimus than tacrolimus
Everolimus to maintain whole blood concentration of 4-8ng/ml and Antithymocyte globulin single dose of 3 mg/kg ³⁰	Everolimus to maintain whole blood concentration of 4-8ng/ml and Basiliximab 2 doses of 20 mg on day 0, 4	Mycophenolate Sodium 1440 mg daily and Basiliximab 2 doses of 20 mg on day 0, 4	Immunosuppressant after kidney transplant	Wound healing adverse events (e.g. dehiscence, healing infection, hernia, fluid collection, etc.)	Incidence of wound healing adverse events was lowest in mycophenolate sodium and Basiliximab and highest in Everolimus and Basiliximab
Basiliximab 2 doses of 20 mg ³¹	Antithymocyte globulin (3-5 mg/kg)		Immunosuppressant after kidney transplant	Wound infections	Incidence of wound infections was approximately equal between two groups
Systemic Tacrolimus 3 mg twice daily then trough levels targeted ³⁶	Sirolimus 10 mg daily x 2 days then 5 mg daily		Immunosuppressant after kidney transplant	Wound healing complications	Significantly higher wound complication rate in sirolimus
MMF 1000 mg every 12 hours ⁴⁶	Sirolimus 15 mg post operatively, then 5mg/day targeting trough of 10-20 ng/mL		Immunosuppressant after kidney transplant	Wound healing complications	Incidence of wound complications was much higher in sirolimus (43.2%) versus MMF (2.4%)
Sirolimus 15 mg load followed by 5 mg/day, MMF 1000 mg/day, Prednisone (doses varied) ⁴⁹	Cyclosporine A 6-8 mg/kg/day, MMF 1000 mg/day, Prednisone (doses varied)	Azathioprine 2-3 mg/kg/day, Cyclosporine A 6-8 mg/kg/day, Prednisone (doses varied)	Immunosuppressant after kidney transplant	A wound was considered healed if after removal of all sutures/staples there was intact skin/tissue without drainage (primary surgical site only)	Differences were not statistically significant when measuring wound healing problems
Everolimus dose to achieve trough concentration of 3-8 ng/mL & reduced exposure to CNI ⁵⁰	MPA 1440 mg/day & standard exposure to CNI		Immunosuppressant after kidney transplant	Adverse events: fluid collections, wound complications, or wound pain	Incidence of wound healing adverse events were relatively similar in both groups
MMF 500-1000 mg/day ⁴⁷	Sirolimus 1-3 mg/day to target a trough of 5-10 ng/mL		Immunosuppressant after heart transplant	Post surgical site wound healing complications or fluid collections	Incidence of post-surgical and deep surgical wound complications were much higher in sirolimus than MMF

Table 2. Overview of Indications and Wound Effects of Various Immunosuppressants

Class of Drug	Drug	Indications	Effect on Wounds
Corticosteroids*	Multiple including hydrocortisone and prednisone	Multiple uses including transplants, endocrine diseases, and autoimmune diseases ⁵¹	Detrimental to wound healing
Calcineurin Inhibitors	Cyclosporine	Kidney transplant ⁵² Autoimmune diseases ⁵²	Unknown, different studies demonstrate varied results
	Systemic Tacrolimus	Heart, kidney, liver transplant ⁵³ Autoimmune diseases ⁵³ Dermatological disease ⁵³ Inflammatory bowel disease ⁵³	Unknown, different studies demonstrate varied results
	Topical Tacrolimus	Atopic dermatitis ¹⁷ Eye diseases ⁵³	Low quality evidence demonstrates that topical tacrolimus is possibly beneficial for wound healing
	Pimecrolimus	Atopic dermatitis ¹⁷	No evidence found
mTOR Inhibitors	Sirolimus ²²	Heart ⁵⁴ and kidney transplant ⁵⁵	Detrimental to wound healing
	Everolimus ²²	Kidney, heart, and liver transplant ⁵⁶ Cancer treatment ⁵⁷	Detrimental to wound healing
Monoclonal Antibodies	Muromonab-CD3 ²²	Liver, heart, and kidney transplant ⁵⁸	No evidence found
	Daclizumab (Zenapax) ²²	Liver, heart, kidney, and lung transplant ⁵⁹ Multiple Sclerosis ⁵⁹	No evidence found
	Basiliximab (Simulect) ²²	Liver, heart, kidney, and lung transplant ⁶⁰ Autoimmune diseases ⁶⁰	No evidence found
	Infliximab (Remicade) ²²	Inflammatory Bowel Disease ⁶¹	Unknown, different studies demonstrate varied results
	Adalimumab (Humira) ²²	Autoimmune diseases such as arthritis, Crohn's disease, psoriasis ⁶²	Not enough evidence to conclude
Polyclonal Antibodies	Antithymocyte Globulin ²²	Kidney transplant ²²	Not enough evidence to conclude
	Rho (D) Immune Globulin ²²	Rh disease ²²	No evidence found
Antiproliferative Agents	MMF ²	Heart, kidney, and lung transplants ^{3,40}	Not enough evidence to conclude
	MPS ²	Kidney transplants ⁴⁰	Not enough evidence to conclude
	Azathioprine ²	Kidney transplant ²² Autoimmune diseases such as Crohn's disease, rheumatoid arthritis, multiple sclerosis ^{22,41} Dermatological conditions ⁶³	No evidence found

*For corticosteroids, search results included articles from 1980 to 2021

activate the immune system.²² A small prospective cohort study among patients with rheumatoid arthritis undergoing orthopedic surgery demonstrated that there was no increased risk of surgical wound infections or healing complications in patients on infliximab compared to conventional therapy.²³ Furthermore, a case report claims that topical infliximab was helpful in healing leg ulcers that were resistant to standard treatment suggesting that inhibiting tumor necrosis factor alpha is helpful to wound healing.²⁴ Similar findings were concluded in a case report for treatment of pyoderma gangrenosum with infliximab resulting in improvement of the ulcer.²⁵ Inhibiting tumor necrosis factor alpha was shown to be further associated with wound healing in venous leg ulcers through the use of Adalimumab systemically.²⁶ However, another study used infliximab on rat abdominal wounds and

demonstrated that the tensile strength was significantly lower in the wounds of rats who had been given infliximab compared to those who were the control.²⁷ Overall, the limited literature on the subject to date suggests clinical outcomes thus far are favorable in terms of wound healing.

Polyclonal Antibodies

Polyclonal antibodies (pAb's) are very similar to mAb's in function, with slightly varied mechanism of action.^{28,29} Unlike mAb's, a group of polyclonal antibodies are created from many different lines of B cells and within the group different pAb's bind to different epitopes of an antigen. In contrast, mAb's come from a single line of B cells and can bind to only one antigen.^{28,29} There are two main pAb's: Antithymocyte Globulin and Rho (D) Immune Globulin.²² Antithymocyte Globulin also known as Antihuman Thymocyte Globulin is most commonly

used as an immunosuppressant after kidney transplantation and works by binding to a variety of lymphocytes and depleting the number of T cells in the body.²² Rho (D) Immune Globulin is used in pregnancies where the mother is Rh- and the fetus is Rh+ and essentially stops the formation of anti Rh- antibodies in the mother.²²

Few studies looking at the effects of pAb's on wound healing were found. Two studies outlined the effects of antithymocyte globulin and Basiliximab. The first study in patients with renal transplants, where both drugs were combined with everolimus, showed higher rates of adverse effects of wound healing in Basiliximab.³⁰ The second study demonstrating that the incidence of wound infections was equal in patients taking Basiliximab versus antithymocyte globulin post renal transplant.³¹ Since white blood cells play a key role in wound healing through secreting necessary cytokines and preventing infection,³² it would be reasonable to hypothesise that antithymocyte globulin will affect wound healing since it reduces the number of white blood cells as well as their regulatory mechanisms.

mTOR Inhibitors

Mechanistic target of rapamycin (mTOR) inhibitors are immunosuppressive drugs that works by interacting with proteins in complex signalling pathways to prevent cells moving into the S phase of the cell cycle and therefore suppressing proliferation.^{3,22} mTOR predominantly targets T cells, but can also affect B cells.³ Interestingly, mTOR can cause an increase of production of certain inflammatory cytokines such as interleukin-6 and decrease production of interleukin-10, an anti-inflammatory cytokine.³ There are two main mTOR inhibitors: sirolimus and everolimus.^{3,22} In general, mTOR inhibitors have a variety of applications including cancer therapy.^{3,22} As an immunosuppressant, they are used after transplants.^{3,22} Everolimus has been shown to inhibit the proliferation of fibroblast in in vitro models³³ suggesting that everolimus could have negative consequences for wound healing since fibroblasts are essential for creating an extracellular matrix and creating a frame for other cells.³⁴ In a study comparing sirolimus and systemic tacrolimus, sirolimus had a wound complication rate of 47% compared to tacrolimus with only 8%.³⁵ This is consistent with another study by Larson et al demonstrating higher wound complications with sirolimus compared to tacrolimus.³⁶ Interestingly, obese patients on sirolimus had very high rates of wound complications leading to the study excluding all patients with obesity.³⁶ In line with previous findings, a study on rats showed that increased sirolimus doses decreases wound strength, which the authors hypothesising this effect may be due to lower levels of VEGF and nitric oxide in rats receiving higher doses of sirolimus.³⁷ In one review authors concluded that mTOR inhibitors are harmful to wound healing in high doses, but seem to have a neutral effect in low doses.³⁸ Given early concerns with mTOR inhibitors and wound healing, regimens using these immunosuppressive agents have evolved with lower doses of the mTOR inhibitors and combination therapy.

In the large TRANSFORM randomised control trial investigators compared everolimus plus reduced dose CNI to mycophenolic acid plus standard dose CNI (standard care) in patients with renal transplants and showed wound related adverse events were not statistically different (20.6% vs 17.3%; RR 1.19 95%CI 0.99 to 1.43).³⁹ One limitation of this study was close monitor of everolimus concentrations and difficulties achieving the targeted plasma concentrations C_0 between 3 and 8 ng/mL.³⁹ Overall, review of the current literature is suggestive that mTOR inhibitors have a detrimental effect on wound healing, especially at higher doses, and that improved dosing regimens may lessen or mitigate this risk.

Antiproliferative Agents

There are three regularly used antiproliferative agents: Mycophenolate mofetil (MMF) and Mycophenolate sodium (MPS) (both inosine monophosphate dehydrogenase (IMPDH) inhibitors) and azathioprine.^{2,40} IMPDH inhibitors have a similar effect to mTOR inhibitors in terms of their mechanism of immunosuppression. In the body, MMF and MPS are converted into mycophenolic acid which blocks a portion of a pathway that is crucial for DNA synthesis, to decrease proliferation of T cells and B cells.^{2,5,40} MMF is used for its immunosuppressive effect in heart, kidney, and lung transplants.^{3,40} MPS is used for kidney transplants.⁴⁰ Azathioprine is used as an immunosuppressive drug for kidney transplants and autoimmune diseases including rheumatoid arthritis, Crohn's disease, and multiple sclerosis.^{22,41} In the body, azathioprine reacts with glutathione and is converted into 6-mercaptopurine after which additional metabolites are generated ultimately blocking purine synthesis and stimulation of T-cells.^{3,22}

When a study compared two different doses of MMF in kidney transplant recipients, incidence of wounds requiring surgical intervention were not significantly different, similarly for wounds treated with local wound care.⁴² Based on review of article titles as part of our search, no studies regarding the sole effect of azathioprine on external wound healing in humans were found. When azathioprine was compared to a placebo in a rat study, the wounds of the rats who were on azathioprine took longer to heal than those on the placebo suggesting that azathioprine can have detrimental effects on wound healing, but the extent that it would affect humans is unclear.⁴³

Anti-metabolite

Methotrexate is a commonly used folate antagonist immunosuppressive agent, with indications in many rheumatologic disorders. It also has antineoplastic activity in higher doses. Upon absorption, it enters the cell and is converted to methotrexate polyglutamates where it competes for dihydrofolate reductase thus preventing the transformation of folic acid for its use in the building of nucleic acids.⁶ Like other agents described, there is experimental animal studies with in vitro studies suggesting impairment in wound healing but these effects have not been borne out in clinical studies, particularly in post-surgical wounds.⁶ Thus, it is recommended this drug be continued postoperatively.

Corticosteroids/Glucocorticoids

Glucocorticoids prevent the formation of inflammatory chemicals like cytokines, cell adhesion molecules, and complement factors.³ By inhibiting interleukin-2 formation, glucocorticoids also prevent T cell proliferation and activation.²² They also impair monocytes and B cells.^{3,22} Glucocorticoids were the first antirejection drug created, but as time has passed, there has been a movement to phase them out due to their serious side effects.^{3,22} There is consensus that glucocorticoids are highly detrimental to wound healing since they interfere with many key stages of wound healing such as collagen deposition and synthesis, angiogenesis, fibroblast proliferation, growth factors, and phagocytosis among others.^{2,3,44,45}

Practical considerations for health care providers

Persons with compromised immune systems (due to medications, co-morbidities or age extremes) require additional considerations for chronic wound management. Specific to immunosuppressive medications, health care providers should take a careful history not only of the medications and dosing (including changes in dosing), but also of the underlying conditions requiring these medications (e.g. autoimmune disorders, organ transplantation). As many immunosuppressive medications can impair wound healing, it is crucial for health care providers to assess healing potential early on to set and manage patient expectations. Early referral to medical or surgical specialists to assist with wound care and a team-based approach will be essential given the increased complexity of these individuals. In some cases where wounds are not healing, alternate goals of care for the wound may need to be set (e.g. maintenance or non-healable) if immunosuppressive doses cannot be reduced (assuming it is contributing to poor healing) and should be done in consultation with their primary or specialist care providers. As individuals and populations with comorbidities live longer, taking care of persons with chronic wounds on immunosuppressive medications will become increasingly common and must be recognised early by the wound care clinicians.

DISCUSSION

With the ongoing advances in medicine, the need for immunosuppression in the context of transplant, autoimmune disease and malignancy has increased. In our review, we highlight the poverty of robust studies in this field and highlighted the mixed effects of various immunosuppression on wound healing. High quality evidence exists with respect to the deleterious effects of glucocorticoid therapy as well as mTOR therapy, particularly sirolimus on wound healing. Furthermore, when 4 studies compared sirolimus to either MMF or systemic tacrolimus, all the studies demonstrated sirolimus to be associated with an increased incidence of wound complications.^{35,36,46,47}

The literature on agents such as systemic CNIs is mixed with some suggesting adverse effects on wounds and others

suggesting benefit, necessitating additional study focusing directly on this question. Newer topical CNIs have shown little impact on delayed wound healing and in some cases benefit, but additional investigation is warranted for their use in chronic wounds directly. Reassuringly, antiproliferative agents, antimetabolite, and newer monoclonal antibiotics have not shown signal toward diminished healing. However, additional study is needed given the poverty of evidence on wound healing in mAB therapy. Overall, our review found the evidence in this area is dated with variable conclusions surrounding the effects of the immunosuppressant on wound healing. In addition, we found little evidence using human subjects. In general, when immunosuppressives are prescribed after transplants to prevent rejection, patients take more than one drug to effectively prevent rejection. Therefore, challenges exist in performing human studies evaluating the effects of individual drugs in isolation.

As we did not conduct a systematic review, certain articles may have been excluded. We did identify a few key reviews before conducting the search and ensured they were present in the search as one form of validation. As well, given the paucity of literature in this area particularly as it relates to the wound care field, a narrative review adds value to educate and increase awareness when working with individuals on these medications.

With the growing need for immunosuppression, additional study in this field is critical. Future directions include conducting more studies in animal subjects with newer classes of immunosuppressants to identify potential pathways to delayed wound healing and potential ways to mitigate such effects. In addition, more high-quality studies are required to evaluate both individual and combination immunotherapies to better understand the risks and how different immunosuppressants may impact wound healing. In order to explore immunosuppressants as a potential treatment for chronic or complex wounds, it is important for future studies to be conducted on a larger scale, control for confounding clinical factors, such as through randomised control trials.

CONCLUSIONS

In conclusion, immunosuppressants range from possibly beneficial to floridly deleterious in wound healing. While there is little conclusive evidence in this field, the effects of immunosuppressants on wound healing is worth exploring to better tailor immunosuppression to patients at risk for or experiencing chronic non-healing wounds. Reassuringly, our findings suggest not all immunosuppressants are harmful with some potentially offering benefit to wound treatment when conventional therapies has failed, opening up the possibility of a new treatment option for wounds.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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