Literature review

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

ABSTRACT

Objective To review 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 The researchers initially screened article titles using key words such as "immunosuppressive medication," "wound healing," and "immunosuppression." Articles in which the title and/or abstract contained these key words, that addressed wound healing related to immunosuppressant medications, and were published after 2000 were included in the review. When human data were not available for an immunosuppressant (class), animal studies were included.

Data Extraction The 61 included articles underwent full text review and summarization.

Data Synthesis: All included studies were summarized descriptively including immunosuppressive mechanism of action, study participants or subjects, and evidence of effects on wound healing.

Conclusions Corticosteroids and mechanistic target of rapamycin inhibitors most consistently demonstrate detrimental effects on wound healing. For other classes of immunosuppressants, evidence is limited with varying effects on wound healing described. Larger, high-quality studies are required to better understand the effects of immunosuppressants, including those with new mechanisms of action, to identify those with the most impact on 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 and 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 (CNIs),[2,4,5] mechanistic target of rapamycin (mTOR) inhibitors,[2,4] monoclonal antibodies (mAbs),[2,4] polyclonal antibodies (pAbs),[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 infection prevention as well as the healing process of wounds; inflammatory effects lead to cellular proliferation and secretion of important intracellular and extracellular components.[6] With immunosuppressants, the immune system is modulated, thus potentially affecting a wound's healing time and susceptibility to infection.[7] With a growing number of patients on immunosuppressing medications, particularly patients postsurgical transplant, the effect of immunosuppressants on wound healing is an important issue. This review article aims to provide clinicians with an understanding of how different classes of immunosuppressants affect wound healing.

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METHODS

The authors conducted a literature search using the generic names of several common immunosuppressants (glucocorticoids/corticosteroids, mTOR inhibitors, methotrexate, mAbs, pAbs, CNIs, mycophenolate, azathioprine), as well as the terms "wound healing" and "immunosuppression." The primary database searched was PubMed, supplemented by Google Scholar and the University of Calgary Health Science Library database. When possible, the search formatted as follows: "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. The search was limited to articles in English published between 2000 and 2021.

The researchers screened article titles and abstracts for relevance. Articles were considered relevant if they compared various immunosuppressants, discussed their effects on wound healing, and measured wound healing or reported deleterious effects on wounds. If search terms did not identify any studies with human participants, the authors then included studies that used animals to evaluate the immunosuppressive effects of a given drug class on wound healing. When no data were available from 2000 onward, researchers conducted a historic search for the relevant immunosuppressive medications.

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

RESULTS

The authors screened 200 article titles and abstracts, and of these, 61 articles were included in the review. Table 1 highlights the results of select clinical and animal studies. The specific indications for various immunosuppressants including their possible impacts on wounds are outlined in Table 2.

Calcineurin inhibitors

Calcineurin inhibitors are used for a variety of autoimmune diseases, organ transplants, dermatologic conditions, and chronic wounds.[32] There are three main types of CNIs: cyclosporine (systemic), tacrolimus (systemic and topical), and pimecrolimus (topical).[33] They 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.[32] Therefore, CNIs disable one of the main arms of the body's adaptive immune response.

Systemic. Few studies have focused on the effects of CNIs 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.[7,34] Willems et al[7] concluded that tacrolimus does not affect wound healing, whereas Schäffer et al[34] concluded that tacrolimus is detrimental to wound healing. In a case report using systemic tacrolimus as a treatment for ulcers in a person with lichen planus and pyoderma gangrenosum, Miller[35] demonstrated treatment success with this therapy.

No recent human studies have investigated the effect of cyclosporine on wound healing, and two studies using rat models yielded contradictory results. These rat studies focused on the effects of cyclosporine on different markers in the body that signify effective wound healing.[36,37] Nemlander et al[36] compared cyclosporine to methylprednisolone and found that cyclosporine A had no suppressive effect on various inflammatory and biochemical markers in comparison with the glucocorticoid therapy. In contrast, Petri et al[37] found that cyclosporine A had a negative effect on other markers within granulation fibroblasts, most notably activin A among procollagen 1, integrin 1, interleukin 6, transforming growth factor 1, and keratinocyte growth factor. In another animal study, Goldberg et al[38] assigned dogs to one of three groups – no immunosuppression, methylprednisolone plus azathioprine, or cyclosporine A – after a lung transplant. They found that cyclosporine A had no significant effect on the healing of the surgical wound as measured by breaking strength in comparison with glucocorticoid and azathioprine immunosuppression. Overall, the literature on systemic CNIs and wound healing is limited with a heterogeneity of comparators and mixed results on wound healing.

Topical. Topical CNIs (tacrolimus and pimecrolimus) are often used for dermatologic conditions such as atopic dermatitis or pyoderma gangrenosum.[20,39,40] Some case studies have shown that tacrolimus is effective at healing complex leg ulcers in the context of venous insufficiency or necrobiosis lipoidica when regular treatment strategies have been ineffective.[41,42] Further, a rat-based study with acute cutaneous injury demonstrated that wounds treated with topical tacrolimus versus control (petrolatum) did not differ in healing speed.[43]

Monoclonal antibodies

There are a variety of different mAb therapies with indications in transplants and autoimmune disorders such as rheumatoid arthritis and psoriasis.[21] In general, mAbs work by binding to different receptors and antigens to inhibit the effect of cytokines and other signal pathways that activate the immune system.[21] In a small prospective cohort study among patients with rheumatoid arthritis undergoing orthopedic surgery, Bibbo and Goldberg[44] found that there was no increased risk of surgical wound infections or healing complications in patients on infliximab versus conventional therapy. Further, Streit et al[45] reported a case in which topical infliximab was helpful in healing leg ulcers that were resistant to standard treatment, suggesting that inhibiting tumor necrosis factor α is helpful for wound healing. Similarly, there was a case report that treated pyoderma gangrenosum with infliximab resulting in ulcer improvement.[46] Inhibiting tumor necrosis factor α was further associated with wound healing in venous leg ulcers through the systemic use of adalimumab.[47] However, a study that used infliximab on rat abdominal wounds found that tensile

Table 1. Select studies comparing the effects of different immunosuppressants on wound healing

Author, Year	Drugs Compared	Purpose of Drug	Outcome Measured	Conclusion
Ormerod et al, 2015[8]	1) Cyclosporine 4-400 mg/kg/d 2) Prednisolone 0.75 -75 mg/kg/d	Treat pyoderma gangrenosum	Speed of healing (cm^2/day)	No measurable difference between drugs
Dean et al, 2004[9]	1) Systemic tacrolimus 3 mg twice daily 2) Sirolimus 10 mg daily x 2 d then 5 mg daily	Immunosuppressant after kidney transplant	Dehiscence, fluid collection, superficial or deep infection, or cellulitis	Wound complications were higher with sirolimus than tacrolimus
Ueno et al, 2017[10]	1) Everolimus to maintain whole blood concentration of 4-8ng/ml and antithymocyte globulin single dose of 3 mg/kg 2) Everolimus to maintain whole blood concentration of 4-8ng/ml and basiliximab 2 doses of 20 mg on days 0, 4 3) Mycophenolate sodium 1,440 mg daily and basiliximab 2 doses of 20 mg on days 0, 4	Immunosuppressant after kidney transplant	Wound healing adverse events (eg, dehiscence, healing infection, hernia, fluid collection, etc.)	Incidence of wound healing adverse effects was lowest with mycophenolate sodium and basiliximab and highest with everolimus and basiliximab
Patel et al, 2011[11]	1) Basiliximab, 2 doses of 20 mg 2) Antithymocyte globulin (3-5 mg/kg)	Immunosuppressant after kidney transplant	Wound infections	Incidence of wound infections was approximately equal between groups
Larson et al, 2006[12]	1) Systemic tacrolimus 3 mg twice daily then trough levels targeted 2) Sirolimus 10 mg daily x 2 d then 5 mg daily	Immunosuppressant after kidney transplant	Wound healing complications	Significantly higher wound complication rate in sirolimus
Valente et al, 2003[13]	1) MMF 1,000 mg every 12 h 2) Sirolimus 15 mg postoperatively, then 5mg/d 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%)
Flechner et al, 2003[14]	1) Sirolimus 15 mg load followed by 5 mg/d, MMF 1000 mg/day, prednisone (doses varied) 2) cyclosporine A 6-8 mg/kg/day, MMF 1,000 mg/day, prednisone (doses varied)	Immunosuppressant after kidney transplant	A wound was considered healed if the primary surgical site was intact without drainage after removal of all sutures/staples	Differences in wound healing were not statistically significant
Citterio et al, 2020[15]	1) Everolimus dose to achieve trough concentration of 3-8 ng/mL and reduced exposure to CNI 2) MPA 1440 mg/d and standard exposure to CNI	Immunosuppressant after kidney transplant	Adverse events: Fluid collections, wound complications, or wound pain	Incidence of wound healing adverse effects were relatively similar in both groups
Kuppahally et al, 2006[16]	1) MMF 500-1,000 mg/d 2) Sirolimus 1-3 mg/day to target a trough of 5-10 ng/mL	Immunosuppressant after heart transplant	Postsurgical site wound healing complications or fluid collection	Incidence of postsurgical and deep surgical wound complications were much higher with sirolimus than MMF

Abbreviations: CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; MPA, mycophenolic acid.

Table 2. Overview of indications and wound effects of various immunosuppressants

Class of Drug	Drug	Indications	Effect on Wounds
Corticosteroids[a]	Multiple including hydrocortisone and prednisone	Multiple uses including transplants, endocrine diseases, and autoimmune diseases[17]	Detrimental to wound healing
Calcineurin inhibitors	Cyclosporine	Kidney transplant[18] Autoimmune diseases[18]	Unknown; different studies demonstrate varied results
	Systemic tacrolimus	Heart, kidney, liver transplant;[19] autoimmune diseases;[19] dermatological disease;[19] inflammatory bowel disease[19]	Unknown; different studies demonstrate varied results
	Topical tacrolimus	Atopic dermatitis;[20] eye diseases[19]	Low quality evidence demonstrates that topical tacrolimus is possibly beneficial for wound healing
	Pimecrolimus	Atopic dermatitis[20]	No evidence found
mTOR inhibitors	Sirolimus[21]	Heart[22] and kidney transplant[23]	Detrimental to wound healing
	Everolimus[21]	Kidney, heart, and liver transplant[24] Cancer treatment[25]	Detrimental to wound healing
Monoclonal antibodies	Muromonab-CD3[21]	Liver, heart, and kidney transplant[26]	No evidence found
	Daclizumab (Zenapax)[21]	Liver, heart, kidney, and lung transplant;[6] multiple sclerosis[26]	No evidence found
	Basiliximab (Simulect)[21]	Liver, heart, kidney, and lung transplant;[6] autoimmune diseases[26]	No evidence found
	Infliximab (Remicade)[21]	Inflammatory bowel disease[27]	Unknown, different studies demonstrate varied results
	Adalimumab (Humira)[21]	Autoimmune diseases such as arthritis, Crohn disease, psoriasis[28]	Not enough evidence to conclude
Polyclonal antibodies	Antithymocyte globulin[21]	Kidney transplant[21]	Not enough evidence to conclude
	Rho (D) immune globulin[21]	Rh disease[21]	No evidence found
Antiproliferative agents	MMF[2]	Heart, kidney, and lung transplants[3,29]	Not enough evidence to conclude
	MPS[2]	Kidney transplants[29]	Not enough evidence to conclude
	Azathioprine[2]	Kidney transplant;[21] autoimmune diseases such as Crohn disease, rheumatoid arthritis, multiple sclerosis;[21,30] skin conditions[31]	No evidence found

Abbreviations: MMF, mycophenolate mofetil; MPS, mycophenolate sodium; mTOR, mechanistic target of rapamycin.
[a]For corticosteroids, search results included articles from 1980 to 2021.

strength was significantly lower in the wounds of rats who had been given infliximab versus control.[48] Overall, the literature is limited but suggests clinical outcomes may be favourable in terms of wound healing.

Polyclonal Antibodies

Polyclonal antibodies are very similar to mAbs in function, with slightly varied mechanism of action.[49,50] Unlike mAbs, a group of pAbs is created from many different lines of B cells, and different pAbs bind to different epitopes of an antigen. In contrast, mAbs come from a single line of B cells and can bind to only one antigen.[49,50]

There are two main pAbs: antithymocyte globulin (also known as antihuman thymocyte globulin) and rho (ρ) immune globulin.[21] Antithymocyte 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.[21] Rho immune globulin is used in pregnancies in which the gestational parent is Rh- and the fetus is Rh+ to essentially stop the formation of anti-Rh+ antibodies in the mother.[21]

Few studies have investigated the effects of pAbs on wound healing. However, two studies outlined the effects

of antithymocyte globulin and basiliximab. Ueno et al[10] investigated the use of these drugs combined with everolimus in patients with renal transplants. They reported higher rates of adverse effects on wound healing with basiliximab.[10] Patel et al[11] demonstrated that the incidence of wound infections was equal in patients taking basiliximab versus antithymocyte globulin after renal transplant. White blood cells play a key role in wound healing by secreting necessary cytokines and preventing infection[51]; thus, it is reasonable to hypothesise that antithymocyte globulin would affect wound healing because it reduces the number of white blood cells and their regulatory mechanisms.

mTOR Inhibitors

Mechanistic target of rapamycin inhibitors interact with proteins in complex signaling pathways to prevent cells from moving into the S phase of the cell cycle and therefore suppressing proliferation.[3,21] Although mTOR predominantly targets T cells, it can also affect B cells.[3] Interestingly, mTOR can increase 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.[3,21] In general, mTOR inhibitors have a variety of applications including cancer therapy and after transplants.[3,21] Everolimus inhibits the proliferation of fibroblasts in in vitro models,[52] suggesting that it could have negative consequences for wound healing because fibroblasts are essential for creating an extracellular matrix and scaffolding other cells.[53] In a study comparing sirolimus and systemic tacrolimus, sirolimus had a wound complication rate of 47%, whereas the rate with tacrolimus was only 8%.[9] This is consistent with another study by Larson et al[12] demonstrating more frequent wound complications with sirolimus compared with tacrolimus. Those authors found that patients with obesity who were on sirolimus had very high rates of wound complications; as a result, the authors excluded all patients with obesity from the study.[12] In line with previous findings, a study on rats showed that increased sirolimus doses decreased breaking strength.[54] The authors hypothesised that this effect may be caused by lower levels of vascular endothelial growth factor and nitric oxide in rats receiving higher doses of sirolimus.[54] In a review article, Nashan and Citterio[55] concluded that mTOR inhibitors are harmful to wound healing in high doses, but seem to have a neutral effect in low does. 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 (Advancing renal TRANSplant eFficacy and safety Outcomes with an eveRoliMus-based regimen) randomised controlled trial, Citterio et al[15] compared everolimus plus reduced-dose CNI with mycophenolic acid plus standard-dose CNI (standard care) in patients with renal transplants. They found that wound-related adverse events did not differ between groups (20.6% vs 17.3%; risk ratio, 1.19; 95% CI, 0.99 to 1.43).[15] One limitation of this study was close monitoring of everolimus concentrations and difficulties achieving the targeted plasma concentrations C_0 between 3 and 8 ng/mL.[15] Overall, the current literature suggests 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), mycophenolate sodium (MPS), and azathioprine.[2,29] Both MMF and MPS are inosine monophosphate dehydrogenase inhibitors. They 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 and B cells.[2,5,29] Whereas MMF is used for its immunosuppressive effect in heart, kidney, and lung transplants,[3,29] MPS is used for kidney transplants.[29] Azathioprine is used as an immunosuppressive drug for kidney transplants as well as autoimmune diseases, including rheumatoid arthritis, Crohn disease, and multiple sclerosis.[21,30] Azathioprine reacts with glutathione in the body and is converted into 6-mercaptopurine. Additional metabolites are then generated, ultimately blocking purine synthesis and T-cell stimulation.[3,21]

In a study comparing two different doses of MMF in kidney transplant recipients, Flechner et al[56] found no significant difference in the incidence of wounds requiring surgical intervention, similarly for wounds treated with local wound care. In analysing article titles for the present review, the authors did not find any studies regarding the sole effect of azathioprine on external wound healing in humans. However, Ginestal et al[57] compared the effects of azathioprine versus placebo in a rat study. They found that the wounds of the rats who were on azathioprine took longer to heal than those on the placebo, suggesting that azathioprine may have detrimental effects on wound healing, but the extent that it would affect humans is unclear.[57]

Antimetabolite

Methotrexate is a commonly used folate antagonist 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] Experimental in vitro animal studies suggest that methotrexate may impair wound healing, but these effects have not been borne out in clinical studies, particularly in postsurgical wounds.[6] Thus, it is recommended that this drug be continued postoperatively.

Corticosteroids/Glucocorticoids

Glucocorticoids prevent the formation of inflammatory chemicals such as cytokines, cell-adhesion molecules, and complement factors.[3] By inhibiting interleukin 2 formation, glucocorticoids also prevent T-cell proliferation and activation.[21] They also impair monocytes and B cells.[3,21] Glucocorticoids were the first antirejection drugs created;

however, there has been a movement to phase them out because of their serious adverse effects.[3,21] Glucocorticoids are highly detrimental to wound healing because they interfere with many key stages, such as collagen deposition and synthesis, angiogenesis, fibroblast proliferation, growth factors, and phagocytosis, among others.[2,3,58,59]

Practical considerations for healthcare providers

Persons with compromised immune systems (due to medications, comorbidities, or age) require additional considerations for chronic wound management. Specific to immunosuppressive medications, healthcare 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 (eg, autoimmune disorders, organ transplantation). Because many immunosuppressive medications can impair wound healing, it is crucial for healthcare 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 is essential, given the increased complexity of caring for these individuals. In cases when wounds are not healing, set alternate goals of care for the wound with the patient (eg, maintenance or nonhealable) if immunosuppressive doses cannot be reduced (assuming it is contributing to poor healing); undertake changes in consultation with the patient's primary or specialist care providers. As individuals and populations with comorbidities live longer, caring for persons with chronic wounds on immunosuppressive medications will become increasingly common and wound care clinicians must be proactive in managing these patients.

DISCUSSION

With the ongoing advances in medicine, the need for immunosuppression in the context of transplant, autoimmune disease, and malignancy has increased. This review highlights the paucity of robust studies in this field and the mixed effects of various immunosuppression on wound healing. High-quality evidence exists with respect to the deleterious effects of glucocorticoid therapy and mTOR therapy (particularly sirolimus) on wound healing. Four studies compared sirolimus with either MMF or systemic tacrolimus, and all four demonstrated that sirolimus was associated with an increased incidence of wound complications.[9,12,13,16]

The literature on agents such as systemic CNIs is mixed, with some suggesting adverse effects on wounds and others suggesting benefits; additional research focusing on this question is needed. Newer topical CNIs have shown little impact on delayed wound healing and, in some cases, may benefit healing, but additional investigation is warranted for their use in chronic wounds directly. Studies indicate that antiproliferative agents, antimetabolites, and newer mABs do not negatively impact wound healing. However, additional research is needed, given the lack of evidence on wound healing in mAB therapy.

Overall, the evidence in this area is limited and draws variable conclusions surrounding the effects of immunosuppressants on wound healing. In particular, few studies have included human participants. 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.

Because this was not a systematic review, the authors may not have identified all relevant articles. However, as one form of validation, the authors identified a few key reviews before conducting the literature search and then ensured these articles appeared in the search as expected. 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 research should investigate newer classes of immunosuppressants in animal models to identify potential pathways to delayed wound healing and potential ways to mitigate such effects. Further, additional high-quality human studies that evaluate both individual and combination immunotherapies are required to better understand the risks and how different immunosuppressants may impact wound healing. To explore immunosuppressants as a potential treatment for chronic or complex wounds, it is important for future studies to be conducted on a large scale and control for confounding clinical factors, such as through randomised controlled trials.

CONCLUSIONS

Immunosuppressants range from possibly beneficial to clearly deleterious in terms of wound healing. There is little conclusive evidence in this field, and the effects of immunosuppressants on wound healing are worth exploring further to better tailor immunosuppression to patients at risk for or experiencing chronic, nonhealing wounds. Some immunosuppressants may offer benefits in wound treatment when conventional therapies have failed, opening up the possibility of a new treatment option for wounds.

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