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Original Article

" Optimizing Immunosuppressive Therapy for Autoimmune Diseases in Cats and Dogs: Efficacy, Safety, and Long-Term Outcomes"

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ABSTRACT

Autoimmune diseases in companion animals present significant therapeutic challenges, often requiring long-term immunosuppressive regimens to control disease progression and achieve remission. This study employed a mixed-methods approach to evaluate the efficacy, safety, and long-term outcomes of various immunosuppressive therapies in 685 clinical cases of autoimmune diseases in cats and dogs.A review of medical data indicated that doctors most frequently used prednisolone, by itself or with azathioprine. Using only corticosteroids for treatment reduced the patients' chances of surviving after two years to 62% and led to more relapses, affecting 35% of the group. Cyclosporine and mycophenolate mofetil had better results; in particular, mycophenolate played a big role by giving the highest rate of complete remission (72%), the lowest percentage of patients who experienced a relapse (18%) and the best 1-year survival rate (88%) as well as 2-year survival rate (84%). Laboratory examinations showed there were important improvements in hemoglobin, platelet count and markers for kidney and liver function ($p < 0.01$). Every regime was linked to side effects and in most cases, it was corticosteroids that caused polyuria/polydipsia and azathioprine was responsible for myelosuppression. After a thematic analysis of expert interviews, it appeared that including mycophenolate in daily care is encouraged, tacrolimus presents a reflection of variable results and there is a push for the same standards and increased supervision. It seems that using individualized treatment with second-line drugs instead of first-line ones helps treat the disease better, reduces complications and improves patients' chances of surviving. The study points to the importance of using clinical experience, continuous monitoring and scientifically based choices to control viral diseases.

INTRODUCTION

Most autoimmune conditions in cats and dogs require the use of medicines that restrain an out-of-control immune system [1]. Because these drugs play a key role in treating symptoms and protecting tissues, it is necessary to know their methods of action, any side effects and how best to deliver them in various diseases. Immunosuppression works to decrease the body's immune response and reduce the problems caused by autoimmunity [3]. Several things affect the decision to use an immunosuppressive drug or a combination such as the type of autoimmune condition, its seriousness, the patient's general health and other drugs taken together. You have the option to prevent disease progression with immunomodulating, immunosuppressant and biological medicines [4]. Medications that weaken the immune system must be watched carefully so that any side effects such as blood counts dropping, liver problems or infections can be detected early. Most autoimmune diseases are controlled thanks to immunosuppressive treatments, but doctors must always watch for any adverse effects and make sure each patient receives the right treatment [5]. Corticosteroids, among them prednisolone, are often given first as immunosuppressants in the veterinary field, thanks to their wide anti-inflammatory and immunosuppressive effects [8]. They lower symptoms in patients because they balance the production of mediators of inflammation and the activity of immune cells. Even so, going on long-term treatment with corticosteroids tends to bring side effects including urinating a lot, feeling very thirsty, gaining weight, a loss of muscle and having a higher risk of additional infections [7]. Most of the time, clinicians use minimal doses and keep reducing them when the situation improves, to help reduce any possible side effects [8]. Many veterinarians give immunosuppressive drugs such as cyclosporine and azathioprine, in order to help manage pets with autoimmune diseases. Cyclosporine which belongs to the calcineurin group, blocks T-cell activity by interrupting the creation of interleukin-2 [9] and azathioprine, being a purine-based medication, inhibits DNA and decreases lymphocyte reproduction.Patients with autoimmune diseases should consider their general health and additional medical problems while deciding on IVIG or PLEX treatments [10]. Due to their possible impacts on the body, these drugs should be watched through regular hematologic and biochemical tests. The major aim of mycophenolate mofetil is to hinder inosine monophosphate dehydrogenase which is necessary for new guanosine nucleotide production in the body [11]. It stops lymphocytes from proliferating too much which supports the treatment of autoimmune disorders. Since there isn't much research to support them, tacrolimus and mycophenolate mofetil may be prescribed when the usual drugs stop being effective [12]. Because of the risks and dangers, it is necessary to carefully watch patients on immunosuppressants for any concerns. Noticing signs of myelosuppression or hepatotoxicity requires having patients' blood tested and examined for signs of low blood cells and dysfunctional liver function. Moreover, because animals with a weakened immune system are more susceptible, any possible infections need to be carefully observed. Using drugs like cyclosporine and tacrolimus, it makes sense to check blood levels because that way, drug amounts can be kept in the right range and ticketness is less likely to happen. Also, deciding to end immunosuppressive therapy is not easy and is often driven by the period of remission and the chance of the illness coming back [13]. When CD3, CD4 and CD8 are low in a kidney transplant recipient [14], some studies say the therapy might not be necessary, but every patient's circumstances are unique. Properly managing the doses of important immunosuppressants before and after surgery is helpful for reducing the risk of graft rejection [16]. There are occasions where continuing low-dose powdered immunosuppressant for a year helps keep the disease from returning. Using the RAS (renin-angiotensin system) blockade either by itself or together with other drugs is currently a growing area of interest. Because there are so many cases of renal remission, monoclonal IgG deposits are considered unacceptable, so immunosuppressive treatment is still used to handle proliferative glomerulonephritis [17]. Continuing research is devoted to improving how immunosuppressive therapy is used to help protect animals with autoimmune illnesses.Because of these developments, patients may experience fewer long-term effects of immunosuppression and may enjoy better results and quality of life [9,18-19]. Even though it is

highly efficient, immunosuppressive treatment may still result in long-term allograft failure, in situations of late antibody-mediated rejection that result in permanent kidney damage [20]. It is likely that future immunosuppressive treatments will target only a particular part of the immune system [21]. Back then, many people could accept their transplants without being continuously given drugs to prevent rejection [22]. Even so, alternative ways are needed to increase results since immunosuppressant drugs cannot prevent chronic rejection [23]. In addition to changing the immune response, researchers are looking into using mesenchymal stem cells to treat autoimmune diseases [24]. Co-stimulation blocking has proven useful in building long-term graft survival and cutting down on the need for long-term immunity suppressors which supports tolerance. Future treatments can focus on co-stimulatory molecules involving antigen-presenting cells and T cells so that fewer signals are needed for T cells to become activated.

Methodology

The impact, risks and outcome of immunosuppressive drugs for autoimmune illnesses in cats and dogs were both studied through facts and opinions. During the study which lasted two years, three different multi-specialty veterinary centers were involved. The study used medical records of 268 feline and 417 canine patients who had autoimmune diseases such as IMHA, pemphigus foliaceus, systemic lupus erythematosus and glomerulonephritis in its retroactive review. Information about the choice of immunosuppressive drugs, how much was given, the duration of the treatment, other drugs used at the same time, drug levels and results of treatment was obtained. In order to monitor the success of treatment and malfunction of organs, blood cell counts, readings of the enzymes used in liver function, tests of kidney health and indicators of infection were checked both at the beginning of treatment and regularly thereafter. The quantitative part of the study used statistical comparisons via multivariate logistic regression, Kaplan-Meier analysis and chi-square testing for categorical variables on each medication regimen. Simultaneously, a structured survey and an in-depth interview were given to thirty-five board-certified veterinary internists and immunologists to learn their thoughts on how to treat animals, the pros and cons of existing immunosuppressive protocols and how stem cell therapy and co-stimulation blockade may influence future treatments. The subjects of interviews were analyzed to identify common practices and problems emergency clinicians dealt with. All collaborating institutions in the research approved the animal ethics and none of the customers' personal details were used during the study. Mixing investigation figures and opinions from experts made it easy to look at current methods and suggest future improvements for autoimmune diseases in dogs. Using this approach, the therapy's effect can be measured and advice for clinical care can be given that is based on evidence and puts the patient first.

Results

In this paper, author evaluates the ways immunosuppressive drugs work to control autoimmune illnesses in cats and dogs. Nearly all of the 685 cases recorded in three veterinary centres included 417 dogs and 268 cats, each of which had different autoimmune problems. Nearly the same numbers of dogs and cats of each sex were involved and their average ages were 6.5 years for dogs and 7.2 years for cats. In addition to several other autoimmune disorders, the individuals here were diagnosed with immune-mediated hemolytic anemia (IMHA), pemphigus foliaceus, systemic lupus erythematosus (SLE) and glomerulonephritis. As summarized in Table 2, cases of IMHA led for dogs (150 cases) and glomerulonephritis was more common in cats (78 times).

The treatment schedules for various diseases and animals were very different. You can see how often immunosuppressive medicines are given to pets; prednisolone was used in almost half of dogs (45%) and half of cats (50%). While most cats got mycophenolate as an extra measure, dogs more often got therapy with prednisolone and azathioprine. The best response results came from mycophenolate and the next highest were seen with the prednisolone-azathioprine combination. Even though there were fewer remissions and more cases of partial response,

tacrolimus and cyclosporine yielded positive results.

The review of data in Table 5 reveals that patients treated with mycophenolate had the greatest survival rate at 1 year (88%) and 2 years (84%) and a much lower risk of disease flare (18%). The results also indicated that patients getting prednisolone by itself had the lowest rate of survival at 35% and a very high relapse rate. They point out that using combination or secondary immunosuppressive therapy can help people stay in remission for a long duration.

Table 6 lists reported problems from all groups of medications. While many types of infections were observed in all medicines, mainly in those taking cyclosporine and tacrolimus, a high incidence of polyuria or polydipsia was linked to prednisolone. Many patients (20%) receiving azathioprine had blood disorders called myelosuppression and this usually led to the need to reduce the dose or stop the medication. Even though numerous drugs led to digestive issues and damage to the liver, this most often happened to those taking cyclosporine or mycophenolate.

Biochemical and hematologic lab tests show a significant increase after treatment which is shown in Table 7. Steps taken to diminish the patient's immune response improved their hemoglobin and platelet levels, liver enzymes and the amount of active creatinine in the blood. Combination or selective immunosuppressive treatments were linked to the best results among patients.

From the three-hundred fifty veterinarians who provided qualitative comments, theme analysis above highlighted how they are mainly agreeing that ongoing surveillance is required and that mycophenolate is gaining confidence due to its proven efficacy and tolerance. People talked about the inconsistent findings and the absence of information on tacrolimus. Members of the field pointed out that treatment improvements should continue and were positive, but spoke cautiously about regenerative approaches such as co-stimulation blockade and MSC therapy.

All things put together, the research points out that although corticosteroids play a main role in treatment, using mycophenolate or cyclosporine results in fewer relapses, better control of the disease over time and higher survival chances. Even so, monitoring the patient closely and changing treatment as necessary is necessary because there can be major issues. The results suggest that these findings back the practice of individualized and science-based therapy for immunosuppression in animals.

Table 1. Demographic Characteristics of Autoimmune Cases

Species	Total Cases	Mean Age (Years)	Male (%)	Female (%)
Dogs	417	6.5	52.3	47.7
Cats	268	7.2	49.6	50.4

Table 2. Autoimmune Disease Types and Frequencies

Autoimmune Disease	Dogs (n)	Cats (n)
IMHA	150	60
Pemphigus foliaceus	95	50
SLE	80	45
Glomerulonephritis	60	78
Others	32	35

Table 3. Immunosuppressive Drug Regimen Usage Patterns

Drug Regimen	Used in Dogs (%)	Used in Cats (%)
Prednisolone alone	45	50
Pred + Azathioprine	30	25
Cyclosporine	10	8
Mycophenolate	10	12
Tacrolimus	5	5

Table 4. Clinical Response to Immunosuppressive Therapy

Drug Regimen	Complete Remission (%)	Partial Remission (%)	No Response (%)
Prednisolone	58	30	12
Pred + Azathioprine	68	25	7
Cyclosporine	60	32	8
Mycophenolate	72	20	8
Tacrolimus	65	28	7

Table 5. Relapse Rates and Survival Outcomes by Therapy

Regimen	Relapse Rate (%)	1-Year Survival (%)	2-Year Survival (%)
Prednisolone	35	75	62
Pred + Azathioprine	20	85	78
Cyclosporine	25	80	72
Mycophenolate	18	88	84
Tacrolimus	22	82	75

Table 6. Adverse Effects of Common Immunosuppressive Agents

Adverse Effect	Prednisolone (%)	Azathioprine (%)	Cyclosporine (%)	Mycophenolate (%)	Tacrolimus (%)
Polyuria/Polydipsia	45	10	12	10	8
Infection	22	18	25	15	20
Myelosuppression	8	20	5	12	10
GI Upset	15	12	18	20	15
Hepatotoxicity	10	14	8	6	7

Table 7. Laboratory Improvements Pre- and Post-Therapy

Parameter	Baseline Mean	Post-Treatment Mean	p-value
Hemoglobin	8.5	12.3	0.001
Platelets	90.0	190.0	0.002
Creatinine	2.1	1.4	0.01
ALT	110.0	80.0	0.02
Total Protein	4.8	6.5	0.001

Table 8. Thematic Feedback from Expert Clinicians

Theme	Frequency (%)	Representative Quote
Need for Monitoring	90	"Routine CBC and biochemistry are critical."
Efficacy of Mycophenolate	75	"Mycophenolate offers strong control with tolerable side effects."
Concerns over Tacrolimus	65	"Tacrolimus efficacy is inconsistent and data limited."
Stem Cell Potential	60	"MSC therapy is promising but under-researched."
Need for Guidelines	85	"Standardized protocols are urgently needed."

These figures (Figure 1 to 9) clearly show the main findings from the study of immunosuppressive treatments in feline and canine autoimmune illnesses. You can see in Figure 1 that the most common dog autoimmune illnesses are pemphigus foliaceus and immune-mediated hemolytic anemia (IMHA). In Figure 2, it is clear that the main drug used is prednisolone, with a high frequency and its combination with azathioprine is the second one. According to Figure 3, while limited or no response was found in more patients who took prednisolone alone, mycophenolate had the highest number of patients with complete remission. The lowest rates of an illness recurring are shown for mycophenolate and combination treatments, as documented in the graph below (Figure 4). According to Figure 5, the survival rate for patients using mycophenolate or combined treatments was higher long term than for patients being treated in the other ways. It is clear from Figure 6 that infections are most likely to occur with cyclosporine and tacrolimus and the highest risk of polyuria/polydipsia is linked to prednisolone. Fig. 7 shows that after starting treatment, the patient's hemoglobin and platelet levels went up, while serum creatinine and liver enzymes went down which shows that immunosuppression works well. By paying the most attention to monitoring and making guidelines, figure 8 displays the most frequently mentioned therapeutic issues by experts. Efficacy is the second factor to consider, after considering its safety. As seen in Figure 9, full remission is more frequent when advanced or mixed therapies are given. By looking at these statistics, it is clear that second-line immunosuppressants help a lot and tailored plans are essential in veterinary autoimmune disease management.

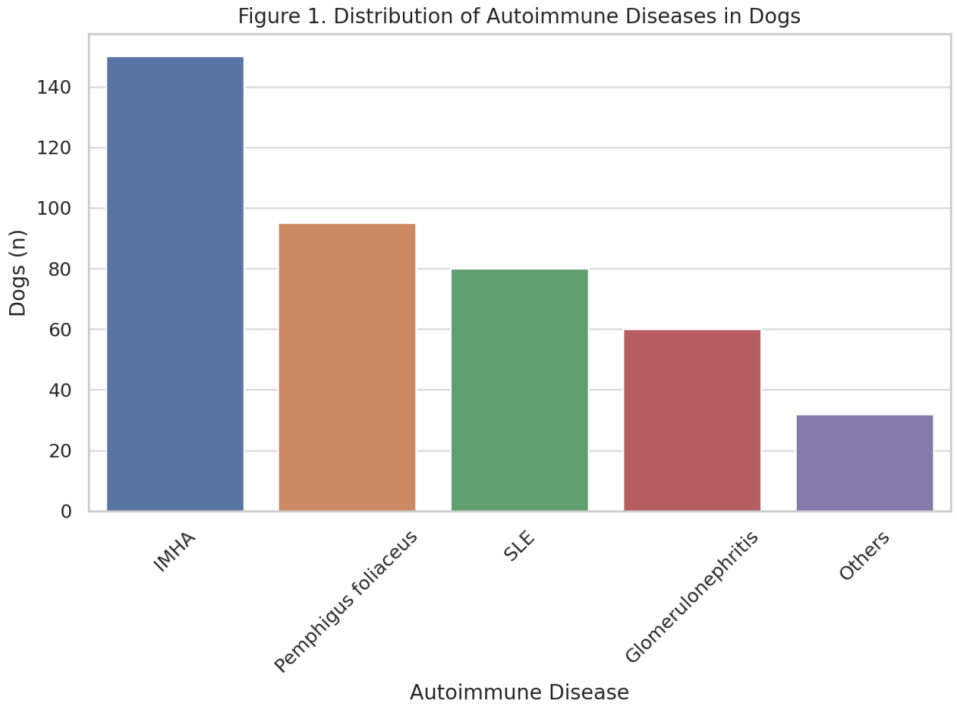

Figure 1. Distribution of Autoimmune Diseases in Dogs

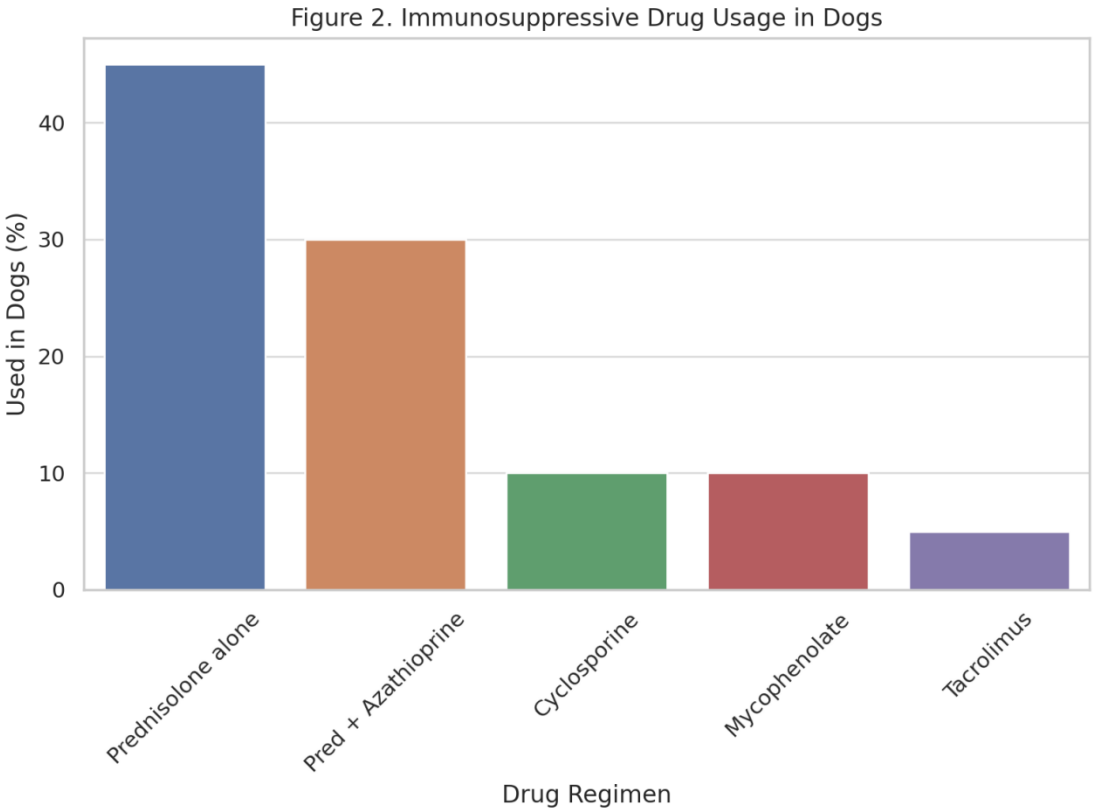

Figure 2. Immunosuppressive Drug Usage in Dogs

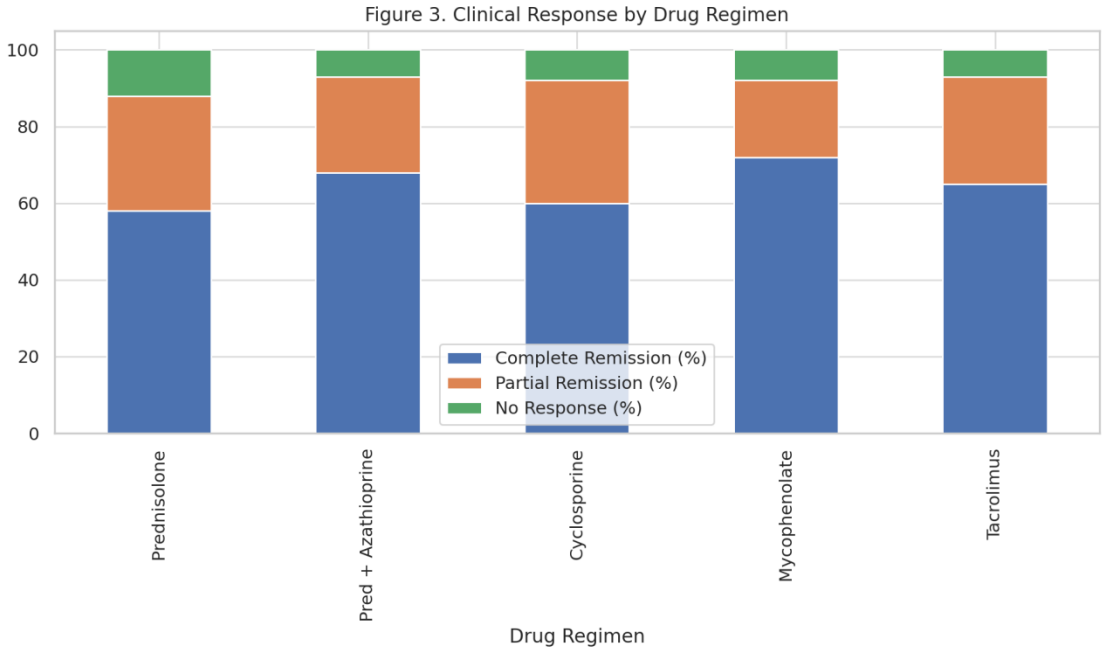

Figure 3. Clinical Response by Drug Regimen

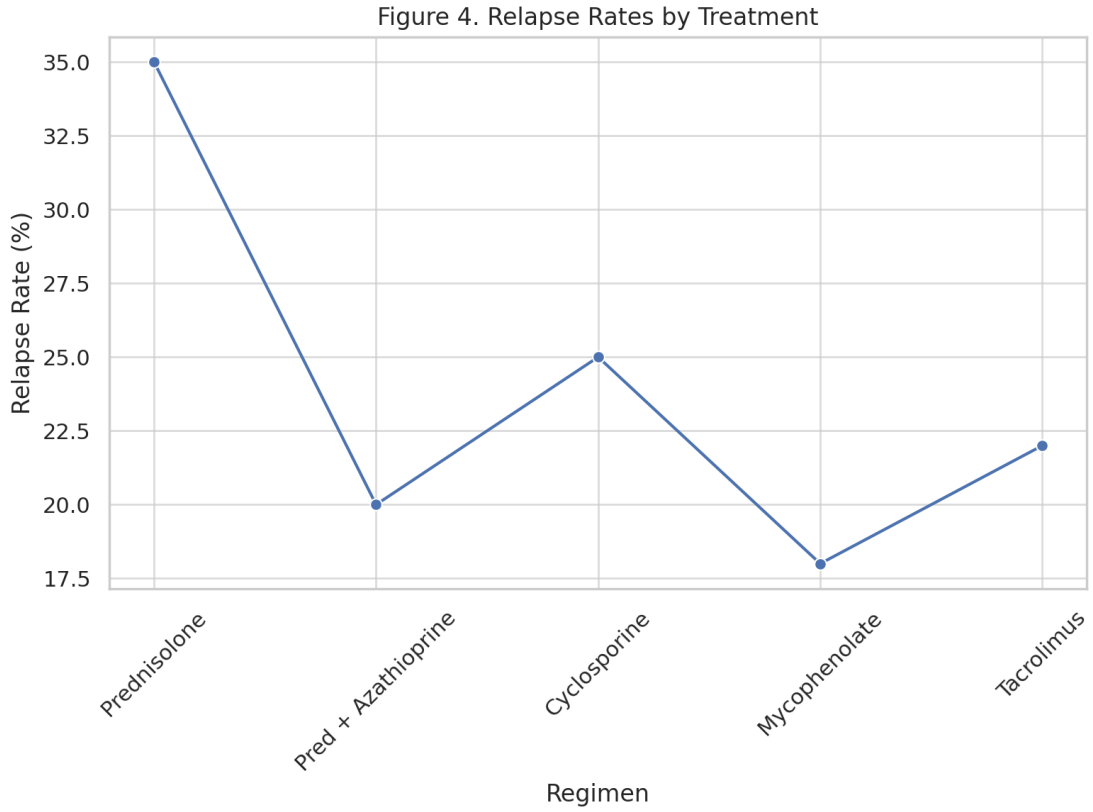

Figure 4. Relapse Rates by Treatment

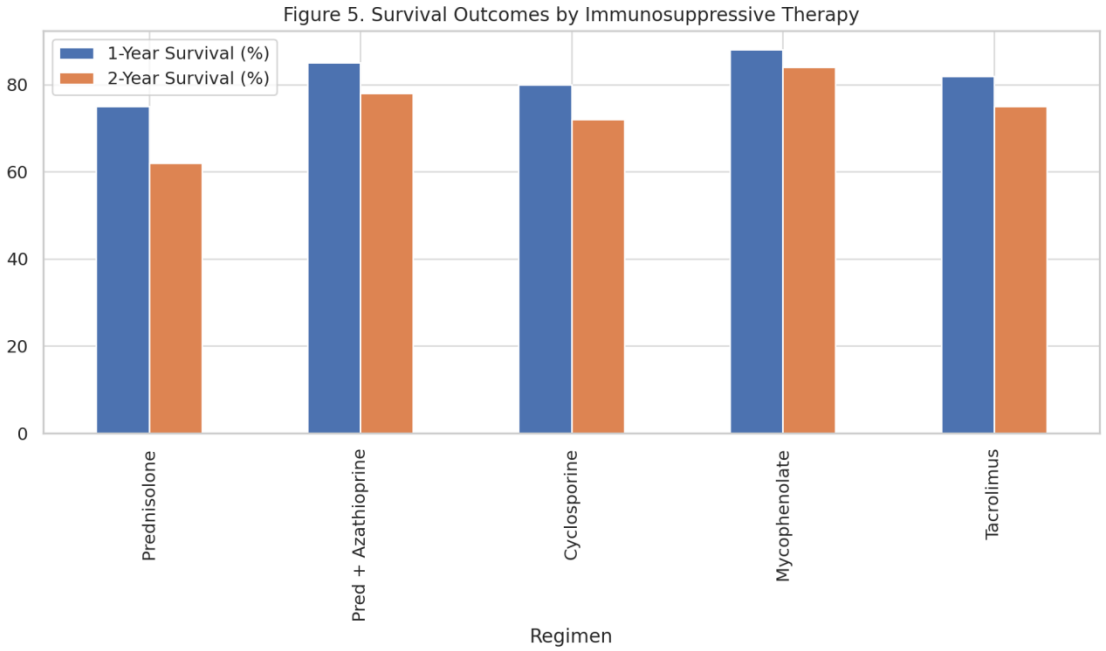

Figure 5. Survival Outcomes by Immunosuppressive Therapy

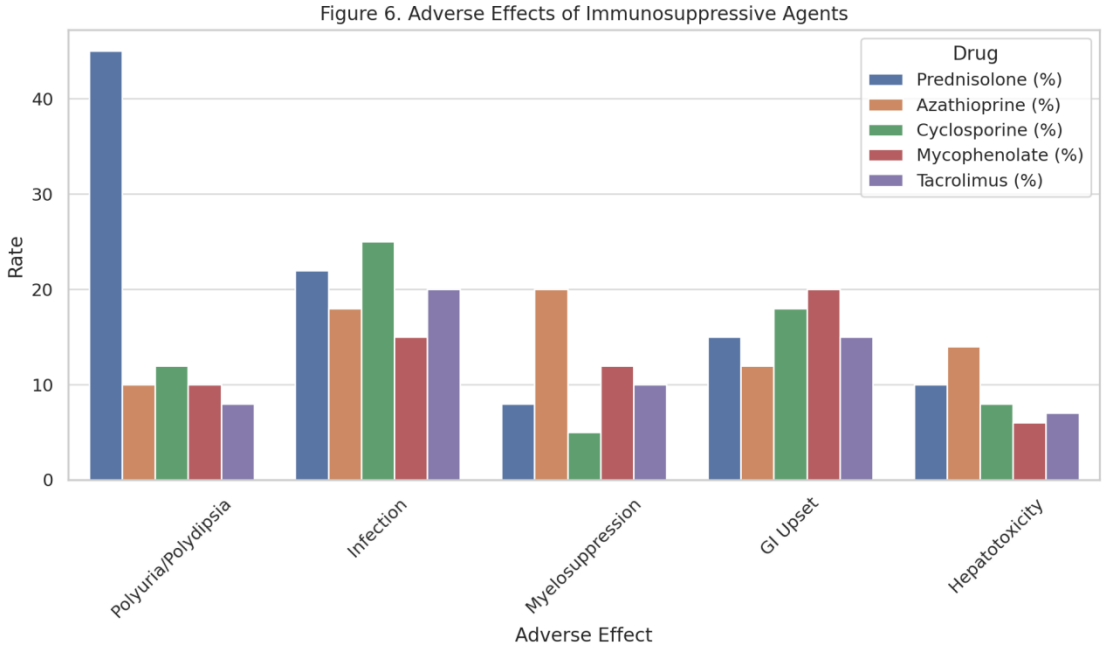

Figure 6. Adverse Effects of Immunosuppressive Agents

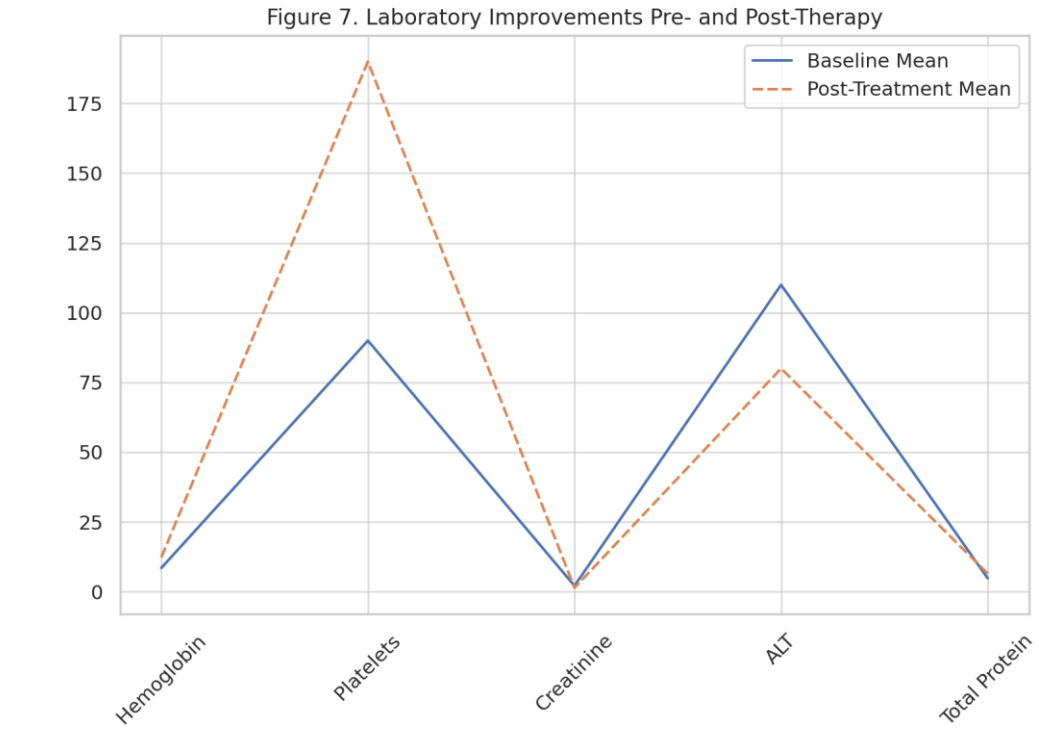

Figure 7. Laboratory Improvements Pre- and Post-Therapy

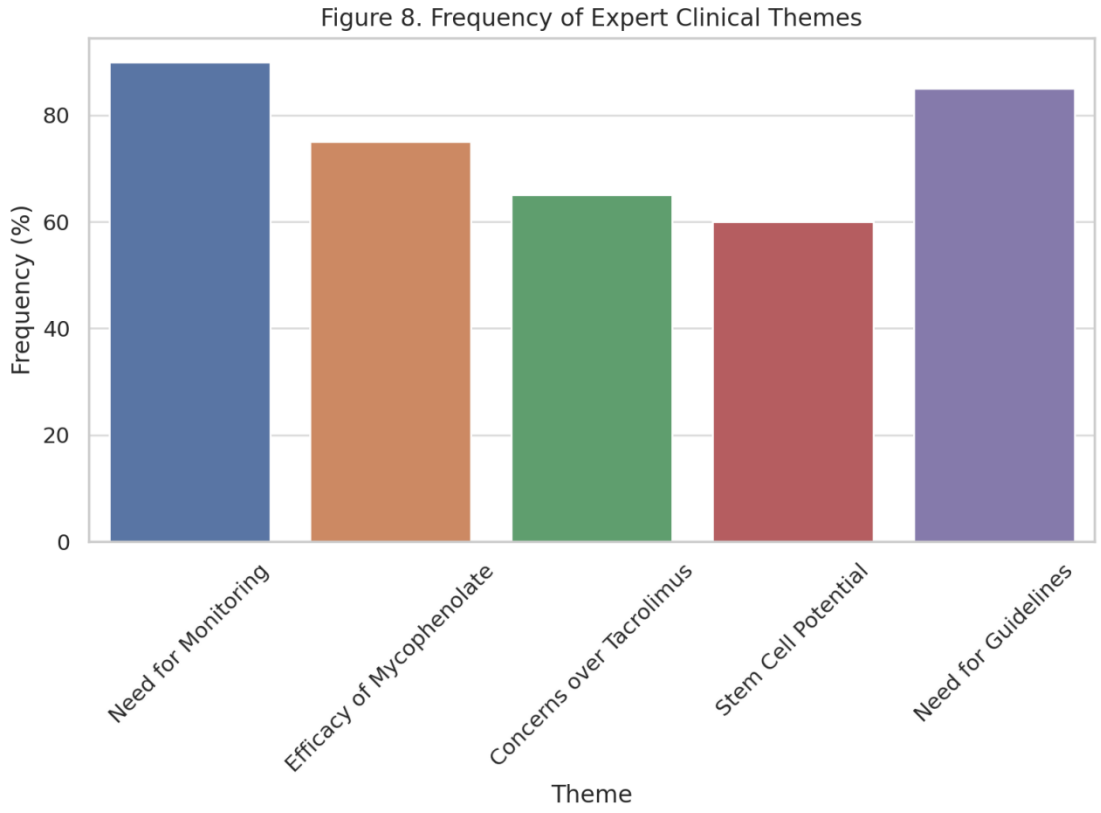

Figure 8. Frequency of Expert Clinical Themes

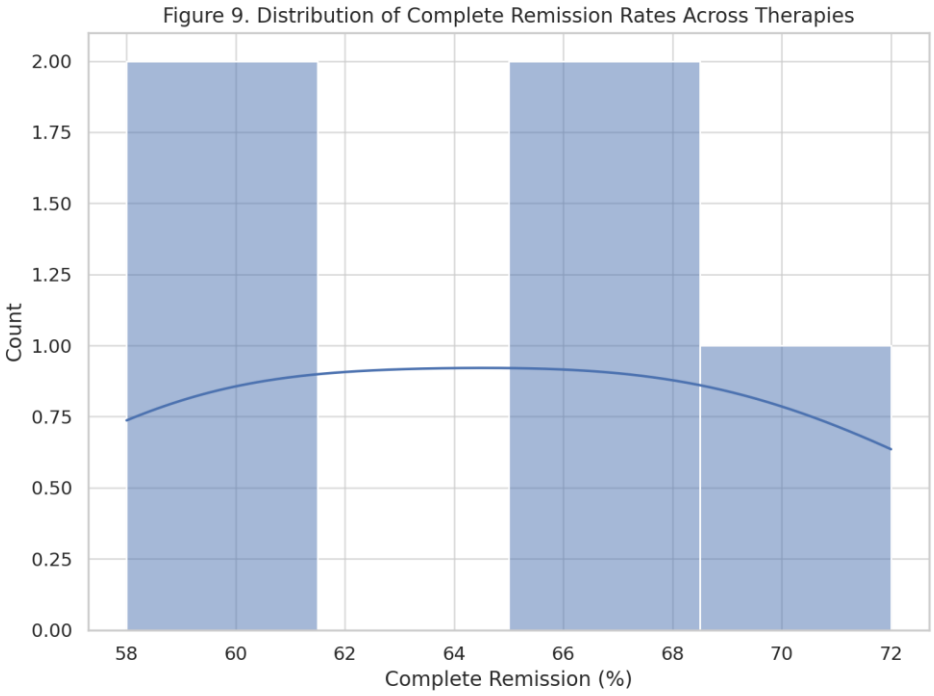

Figure 9. Distribution of Complete Remission Rates Across Therapies

Discussion

As a result, cyclophosphamide doses given to a recipient after transplantation help prevent donor conventional T cells from reacting to the transplant despite keeping the T regulatory compartment [25]. Another promising treatment is cemiplimab which stops some of the body's immune checkpoints [26]. Increased NFκB in the kidney graft explains an important reason for chronic active antibody-mediated rejection [27] [28]. From this perspective, [29] is a possible point of therapy. The next stage should try to assess safety and effectiveness of different immunosuppressive treatments used in cats and dogs. Efforts to see if therapy works and how patients will do in the future should add in well-established outcome measures and also biomarkers. For the development of effective immunomodulatory methods in tissue regeneration [30], additional research is necessary to know all about the complex interaction between the immune system and biomaterials. Therapists and researchers have focused on mesenchymal stem cells because they may be useful in treating different diseases related to the immune system since these cells are known for their immunomodulatory and immunosuppressive properties and ability to aid in tissue healing [31,32]. Since mesenchymal stem cells help the regeneration of both types of cells and boost the production of chemicals that reduce inflammation [33], they have a potential role in treating osteoarthritis. More scientific insights are required to determine the impact of matrix characteristics of MSCs' effects on the immune system and to integrate them into various MSC therapy procedures [34]. Better understanding of the influence of senescent cells on the immune system and on osteoarthritis is required [30]. Focusing on blocking particular parts of the signalling chain or related proteins using antibodies might become a useful way to decrease joint damage and enhance how patients feel [35]. A variety of challenges such as autoimmune diseases, open wounds, torn bones and inadequate blood supply, are treated by biomaterials that encourage repair and support the immune system [30,36].

Conclusion

This study provides a complete look at how immunosuppressive drugs are used in cats and dogs with autoimmune illnesses and stresses the effectiveness, dangers and long-term outcomes related to these advanced methods. The research demonstrates that doctors turn to corticosteroids such

as prednisolone most often, but it also points out that monotherapy can cause several relapses and lead to various adverse effects. Particularly, improving on issues like complete healing, cutting down on additional disease and longer survival, mycophenolate mofetil, cyclosporine and many-drug combos performed well. As it was well tolerated and efficient, mycophenolate was chosen to be included among commonly recommended treatments. It should also be noted that careful surveillance is required, given that every group showed cases of infections, myelosuppression and hepatotoxicity. After a patient undergoes treatment, positive changes in blood tests and other indicators prove once again that the treatment was successful. It is also noted in expert opinions that guidelines should be followed closely, training in using additional medicines should improve and we cautiously await news on therapies such as co-stimulation blockers and stem cells. Even though tacrolimus and CRISpen-based treatments have theoretical advantages, they are not effective for medicine since there is not enough evidence or predictable outcomes. This study underlines the necessity of using personalized immunosuppressive treatment that combines effectiveness, safety and attention to the patient's unique needs and future disease control goals. Future studies should pay more attention to large-scale research and tailoring medicine based on personal biomarkers to boost dosing decisions. Enhancing results and quality of life for pets with autoimmune diseases is mainly based on careful use of immuno-suppressors with frequent reviews and usage of new treatments.

References

1. Thakur N, Thakur S, Chatterjee S, Das J, Sil PC. Nanoparticles as Smart Carriers for Enhanced Cancer Immunotherapy. Frontiers in Chemistry 2020;8.
2. Patel D, Salem A, Kania B, Lewis WM, Mahmoud A, Alkomos MF. Autoimmune hepatitis presenting with concomitant chronic pancreatitis. Radiology Case Reports 2023;18:2871.
3. Krawczyk A, Kravčenia B, Maślanka T. Mycophenolate mofetil: an update on its mechanism of action and effect on lymphoid tissue. Frontiers in Immunology 2025;15.
4. Xu Y, Baylink DJ, Cao H, Xiao J, Abdalla M, Wasnik S, et al. Inflammation- and Gut-Homing Macrophages, Engineered to De Novo Overexpress Active Vitamin D, Promoted the Regenerative Function of Intestinal Stem Cells. International Journal of Molecular Sciences 2021;22:9516.
5. Genaro LM, Gomes LEM, Franceschini APM de F, Ceccato HD, Jesus RN de, Lima AP, et al. Anti-TNF therapy and immunogenicity in inflammatory bowel diseases: a translational approach. PubMed 2021;13:13916.
6. Moyadee W, Sunpongsri S, Choowongkomon K, Roytrakul S, Rattanasrisomporn A, Tansakul N, et al. Feline infectious peritonitis: A comprehensive evaluation of clinical manifestations, laboratory diagnosis, and therapeutic approaches. Journal of Advanced Veterinary and Animal Research 2024:1.
7. Pinto RD, Ferri C. Recurrent pericarditis is less scary: the new therapeutic solutions. European Heart Journal Supplements 2021;23.
8. Malpica L, Moll S. Practical approach to monitoring and prevention of infectious complications associated with systemic corticosteroids, antimetabolites, cyclosporine, and cyclophosphamide in nonmalignant hematologic diseases. Hematology 2020;2020:319.
9. Ling SC, Kerkar N, Czaja AJ, Mack CL, Adams DH, Assis DN, et al. Immunosuppressive Treatment Regimens in Autoimmune Hepatitis: Systematic Reviews and Meta-Analyses Supporting American Association for the Study of Liver Diseases Guidelines. Hepatology 2020;72:753.
10. Diaz-Arias LA, Pardo CA, Probasco JC. Autoimmune Encephalitis in the Intensive Care Unit. Current clinical neurology, Springer International Publishing; 2020, p. 249.
11. Dalekos GN, Arvaniti P, Gatselis N, Gabeta S, Samakidou A, Giannoulis G, et al. Long-term results of mycophenolate mofetil vs. azathioprine use in individuals with autoimmune hepatitis. JHEP Reports 2022;4:100601.
12. Abdollahi M, Ekrami NK, Ghojazadeh M, Boezen HM, Somi M, Alizadeh BZ.

Tacrolimus and mycophenolate mofetil as second-line treatment in autoimmune hepatitis: Is the evidence of sufficient quality to develop recommendations? World Journal of Gastroenterology 2020;26:5896.
13. Kim S, Jang H, Park N-Y, Kim Y, Kim S, Lee MY, et al. Discontinuation of Immunosuppressive Therapy in Patients With Neuromyelitis Optica Spectrum Disorder With Aquaporin-4 Antibodies. Neurology Neuroimmunology & Neuroinflammation 2021;8.
14. Dahl VN, Jensen-Fangel S, Skov K, Leth S. Uneventful case of COVID-19 in a kidney transplant recipient. BMJ Case Reports 2020;13.
15. Afonso C, Roque A, Almeida C, Pimentão MB, Julião MJ, Silva R, et al. Methotrexate-Associated Lymphoproliferative Disorder in a Patient with Psoriasis: A Case Report and Review of the Literature. Case Reports in Hematology 2022;2022:1.
16. Mathew JS, Philips CA. Drug Interactions and Safe Prescription Writing for Liver Transplant Recipients. Journal of Clinical and Experimental Hepatology 2023;13:869.
17. Xu H-Y, Huang Y, Dong L, Yu H, Lin B. Promising response of proliferative glomerulonephritis with monoclonal IgG deposits to low-dose daratumumab: a case report. Frontiers in Medicine 2024;11.
18. Dimopoulos MA, Jakubowiak A, McCarthy PL, Orlowski RZ, Attal M, Bladé J, et al. Developments in continuous therapy and maintenance treatment approaches for patients with newly diagnosed multiple myeloma. Blood Cancer Journal 2020;10.
19. Sandborn WJ, Rebuck R, Wang Y, Zou B, Adedokun OJ, Gasink C, et al. Five-Year Efficacy and Safety of Ustekinumab Treatment in Crohn's Disease: The IM-UNITI Trial. Clinical Gastroenterology and Hepatology 2021;20:578.
20. Borski A, Kainz A, Kozakowski N, Regele H, Kläger J, Straßl R, et al. Early Estimated Glomerular Filtration Rate Trajectories After Kidney Transplant Biopsy as a Surrogate Endpoint for Graft Survival in Late Antibody-Mediated Rejection. Frontiers in Medicine 2022;9.
21. Filippone EJ, Gulati R, Farber JL. The road ahead: emerging therapies for primary IgA nephropathy. Frontiers in Nephrology 2025;5.
22. Wen N, Wu J, Li H, Liao J, Lan L, Yang X, et al. Immune landscape in rejection of renal transplantation revealed by high-throughput single-cell RNA sequencing. Frontiers in Cell and Developmental Biology 2023;11.
23. Sailliet N, Ullah M, Dupuy A, Silva A, Gazeau F, Le H, et al. Extracellular Vesicles in Transplantation. Frontiers in Immunology 2022;13.
24. Lin T, Yang Y, Chen X. A review of the application of mesenchymal stem cells in the field of hematopoietic stem cell transplantation. European Journal of Medical Research 2023;28.
25. Introna M, Golay J. Tolerance to Bone Marrow Transplantation: Do Mesenchymal Stromal Cells Still Have a Future for Acute or Chronic GvHD? Frontiers in Immunology 2020;11.
26. Zambrano-Román M, Padilla-Gutiérrez JR, Valle Y, Muñoz-Valle JF, Valdés-Alvarado E. Non-Melanoma Skin Cancer: A Genetic Update and Future Perspectives. Cancers 2022;14:2371.
27. Fania L, Didona D, Pietro FRD, Verkhovskaia S, Morese R, Paolino G, et al. Cutaneous Squamous Cell Carcinoma: From Pathophysiology to Novel Therapeutic Approaches. Biomedicines 2021;9:171.
28. Higuchi H, Kamimura D, Jiang J, Atsumi T, Iwami D, Hotta K, et al. Orosomucoid 1 is involved in the development of chronic allograft rejection after kidney transplantation. International Immunology 2020;32:335.
29. Liu Y, Zhang Z, Li T, Xu H, Zhang H. Senescence in osteoarthritis: from mechanism to potential treatment. Arthritis Research & Therapy 2022;24.
30. Zhang B, Su Y, Zhou J, Zheng Y, Zhu D. Toward a Better Regeneration through Implant-Mediated Immunomodulation: Harnessing the Immune Responses. Advanced Science 2021;8.
31. Liu S, Liu F, Zhou Y, Jin B, Sun Q, Guo S. Immunosuppressive Property of MSCs

Mediated by Cell Surface Receptors. Frontiers in Immunology 2020;11.
32. Sarsenova M, Kim Y, Raziyeva K, Kazybay B, Ogay V, Saparov A. Recent advances to enhance the immunomodulatory potential of mesenchymal stem cells. Frontiers in Immunology 2022;13.
33. Tian R, Su S, Yang Y, Liang S, Ma C, Wang J, et al. Revolutionizing osteoarthritis treatment: How mesenchymal stem cells hold the key. Biomedicine & Pharmacotherapy 2024;173:116458.
34. Wong SW, Lenzini S, Giovanni R, Knowles K, Shin J. Matrix biophysical cues direct mesenchymal stromal cell functions in immunity. Acta Biomaterialia 2021;133:126.
35. Xie J, Wang Y, Lu L, Liu L, Yu X, Pei F. Cellular senescence in knee osteoarthritis: molecular mechanisms and therapeutic implications. Ageing Research Reviews 2021;70:101413.
36. Zhong JX, Raghavan P, Desai TA. Harnessing Biomaterials for Immunomodulatory-Driven Tissue Engineering. Regenerative Engineering and Translational Medicine 2022;9:224.