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Review Article

Novel intercepts for Multiple Myeloma

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ABSTRACT

The median survival of patients with newly diagnosed MM was approximately 2.5 years, before the introduction of Proteasome inhibitors and immunomodulators. Bortezomib, thalidomide, lenalidomide, and the introduction of autologous stem cell transplantation (ASCT) have substantially improved overall survival (OS), which now ranges from 5 to 7 years.
Several three-drug (triplet) combination regimens have shown better efficacy in, multiple myeloma. Currently, many MM cell antigens, such as daratumumab which is targeted therapy, vaccines (dendritic cell, myeloma derived protein and peptides) are combined with autologous stem cell transplantation. Treatment of Multiple myeloma expensive ranging between 11000 to 13000 USD.

1. Introduction

Multiple myeloma (MM) is a plasma cell dyscrasia characterized by monoclonal plasma cells proliferation in bone marrow, resulting in an overabundance of monoclonal paraprotein (M protein), destruction of bone, and displacement of other hematopoietic cell lines.[1] In India prevalence is in 1.4/1,00,000 population with incidence of 6000 new cases/year.[2] The overall 5-year survival rate for people with multiple myeloma is 54%. Survival rates though have steadily increased over time. Risk factors of multiple myeloma include age > 65 years, male, family history, over weight or obese , radiation exposure, contact with nearly 40 chemicals.[3] Common symptoms may include, bone pain, often in the back or ribs, fractures, weakness or fatigue, weight loss, frequent infections and fevers, feeling thirsty and frequent urination. The diagnostic criteria for multiple myeloma require confirmation of (a) one major criterion and one minor criterion or (b) three minor criteria in an individual who has signs or symptoms of multiple myeloma.

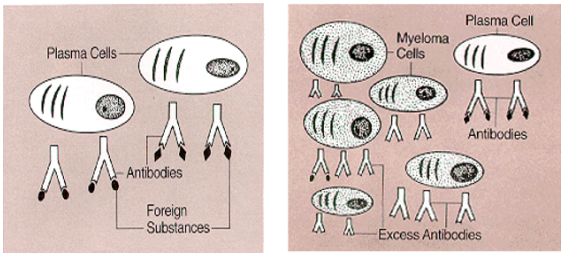

Fig. 1: Pathogenesis of multiple myeloma[4]

1.1. *Radiographic features*

Numerous, well-circumscribed, lytic bone lesions, punched out lucencies and raindrop skull , endosteal scalloping can be visualized. Vertebral compression fractures , long bone fractures are also seen. The predominant areas of bone disease involvement are the axial skeleton, including the vertebral bodies (49%), skull (35%), pelvis (34%), and ribs (33%), and the proximal metaphysis of long bones, especially the femur and humerus[5]

Staging of multiple myeloma: Early : Asymptomatic:

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Table 1: Types of diagnostic criteria

Major Criteria	Minor Criteria
Plasmacytoma	10% to 30% plasma cells in a bone marrow
>30% plasma cells in a bone marrow	Osteolytic lesions, cortical bone damage following osteoporosis.
Slightly elevated levels of M protein in the blood or urine	Presentation of signs, such as bone pain

In healthy bone marrow, < 5% of the cells are plasma cells, whereas in people with MM, > 10 % of the cells may be plasma cells.

This means the person does not have symptoms and signs of the disease. Late: Symptomatic Calcium levels are increased, which is known as hypercalcemia. Calcium level greater than 0.25 mmol/L. Renal, or kidney, problems, identified as a creatinine level higher than 173 mmol/L. Hemoglobin level that is less than 10 g/dl and Bone lesions(known as as CRAB).[6]

2. Drugs for Managing Multiple Myeloma

Bortezomib is a dipeptide boronic acid derivative and proteasome inhibitor used to treat multiple myeloma. Complete remission (CR) or very good partial remission (VGPR) has been observed in multiple myeloma (MM) therapy.

Proteasomes are large protein complexes inside cells they degrade misfolded proteins The 26S proteasome is a protein complex that degrades ubiquitinated proteins in the ubiquitin-proteasome pathway: reversible inhibition of the 26S proteasome, leading to cell cycle arrest and apoptosis of cancer cells, is thought to be the main mechanism of action of bortezomib.

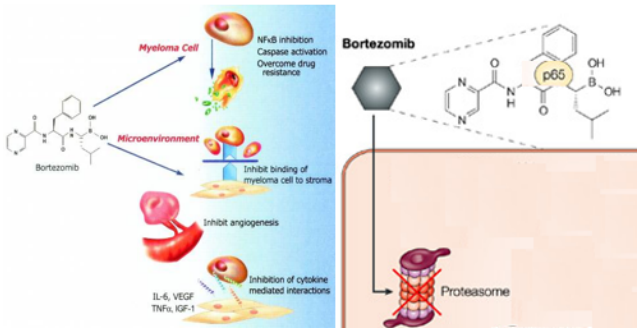

Fig. 2: Mode of action of bortezomib

The mechanism of action of bortezomib involves stabilization of NF-κB, p21, p27, p53, Bid, and Bax, inhibition of caveolin-1 activation, and activation of JNK as well as the endoplasmic reticulum stress response.[10] Subcutaneous administration of bortezomib appears to be comparable with intravenously administered bortezomib in terms of overall systemic availability and response rates in multiple myeloma, but may have an improved safety profile, with fewer dose reductions and discontinuations due to adverse events. Peripheral neuropathy and thrombocytopenia are the key dose-limiting toxicities of bortezomib-based combination regimens.

Carfilzomib irreversibly binds to the active sites of the 20S proteasome, as well as the core component within the 26S proteasome. It has activity bortezomib-resistant cell lines and primary multiple myeloma (MM) cells Used in combination with dexamethasone or with lenalidomide plus dexamethasone or with daratumumab and dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.[11]

2.1. Immunomodulatory drugs: (Lenalidomide, Pomalidomide, Thalidomide)

Their mechanism of action is not exactly clear , but it is known that they inhibit the production of tumour necrosis factor, interleukin 6 and immunoglobulin G and VEGF (which leads to its anti-angiogenic effects), co-stimulates T cells and NK cells and increases interferon gamma and interleukin 2 production . IMiDs, enhances NK-cell cytotoxicity and antibody-dependent cell-mediated cytotoxicity (ADCC) in MM cells. These drugs also downregulate tumor necrosis factor also appears to augment NK cell activity via a variety of mechanisms. Lenalidomide can cause significant neutropenia and thrombocytopenia, pulmonary embolism (PE) in patients with multiple myeloma

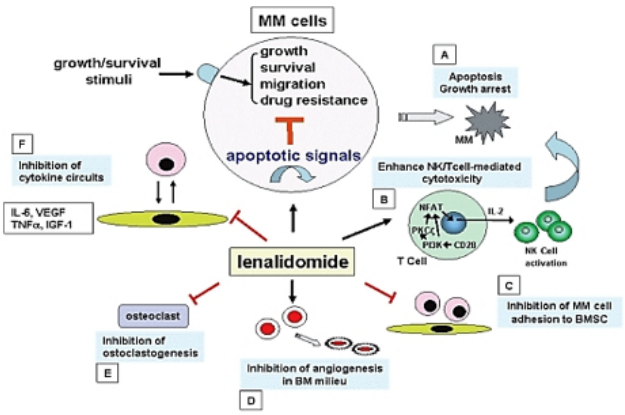

Fig. 3: Mode of action of IMIDs[12]

Table 2: Progressive stages of multiplemyeloma[7]

MGUS = monoclonal gammopathy of undetermined significance.	**SMM = smouldering multiple myeloma.**	**MM = multiple myeloma**
M-protein <30 g/L in the serum	Serum M-protein ≥30 g/L, and/or urine M-protein ≥500 mg/24 h, and/or bone marrow clonal plasmacytosis 10 - 60%	Clonal bone marrow plasmacytosis ≥10% or biopsy-proven plasmacytoma
<10% clonal plasma cells in the bone marrow Absence of myeloma-defining events or amyloid	Absence of myeloma-defining events or amyloid	Bone lesions: ≥1 osteolytic lesion(s) on skeletal survey >1 focal lesion on MRI >1 focal lesion on MRI

Table 3: Classification of drugs[8]

Drug Class	**Examples**
Proteasome Inhibitors	Carfilzomib, Bortezomib, Ixazomib
Immunomodulatory drugs	Thalidomide, Lenalidomide, Pomalidomide
Histone deacetylase inhibitors	Vorinostat, Romidepsin, Panobinostat, and Belinostat
Antitumor antibiotics	Doxorubicin
Alkylating agents	Melphelan, Cyclophosphamide, Bendamustine
Monoclonal antibodies	Daratumumab Elotuzumab

Table 4: Types of proteasomes[9]

Proteasome inhibitor	**Chemical class**	**Binding Kinetics**	**Half Life in minutes**	**Maximal proteasome inhibition at Maximum tolerated dose (%)**
Bortezomib	Boronate IV or SC	Reversible	110	65-75
Carfilzomib	E;poxyketone IV	Irreversible	<30	>80
Ixazomib	Boronate oral	Reversible	18	73-99
Oprozomib	Epoxyketone Oral	Irreversible	30-90	>80
Marizomib	B – Lactone Oral or IV	Irreversible	10-15	100

Panobinostat is a potent oral nonselective pan-histone deacetylase inhibitor (HDAC). It is used in combination with bortezomib and dexamethasone for the treatment of multiple myeloma, in patients who have received at least two prior regimens, including bortezomib and an immunomodulatory agent. Panobinostat inhibits class I (HDACs 1, 2, 3, 8), class II (HDACs 4, 5, 6, 7, 9, 10) and class IV (HDAC 11) proteins.[13] It is administered orally at a starting dose of 20 mg three times a week for 2 weeks every 3 weeks. It is given in combination with bortezomib and dexamethasone. Thrombocytopenia, neutropenia, fatigue, electrolyte abnormalities, and increased creatinine are adverse effects of Panobinostat. Panobinostat prescribing information has a boxed warning, describing a 25% incidence of grade 3–4 diarrhoea.[14]

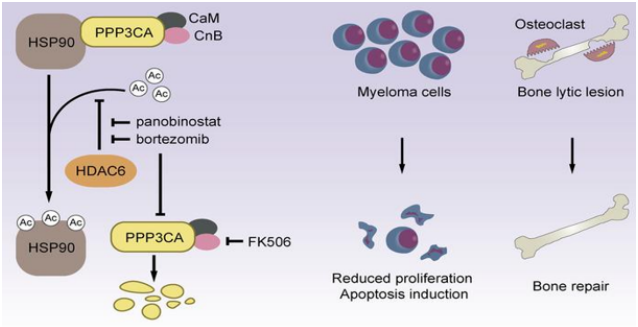

Fig. 4: Mode of action of panobinostat

3. Doxorubicin

Is used in combination with (bortezomib) for the treatment of patients with multiple myeloma who have not previously received bortezomib and have received at least one prior therapy. Doxorubicin inhibits the enzyme topoisomerase II, causing DNA damage and induction of apoptosis. The liposomal formulation of doxorubicin has FDA approval for the treatment of ovarian cancer in patients who have failed platinum-based chemotherapy, AIDS-related Kaposi sarcoma, and multiple myeloma

Fatigue, alopecia, nausea and vomiting, and oral sores and bone marrow suppression are common side effects.[15]

4. Alkylating Agents

Bendamustine is a purine analogue similar to cladribine and fludarabine, which has proven activity in

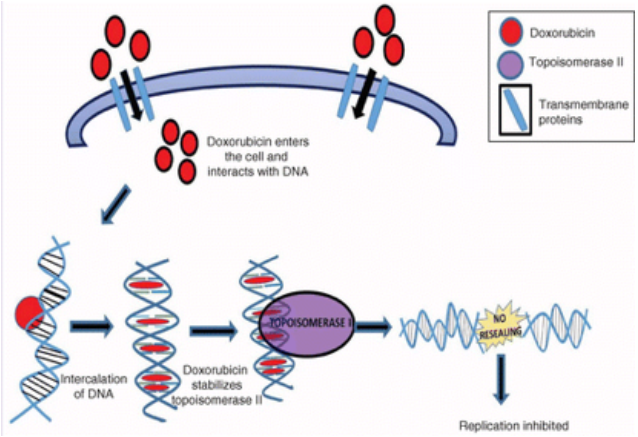

Fig. 5: Action of doxorubicin

both newly diagnosed and relapsed-refractory MM, also in patients above 65 years of age. Bendamustine has also demonstrated activity in MM after relapse from ASCT (Autologous stem cell transplant) and has recently been used successfully as a conditioning regimen for ASCT in combination with melphalan. PFS and the OR rate were at least 2-fold greater with bendamustine than with chlorambucil [16]

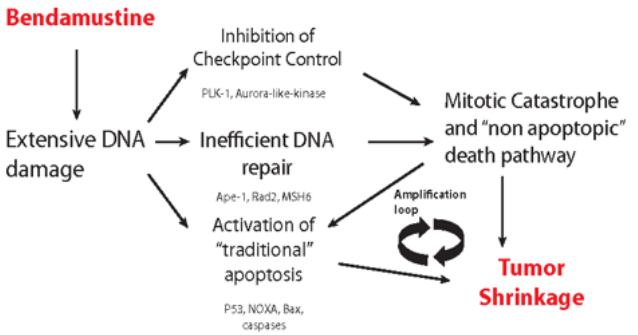

Fig. 6: Mode of action ofbendamustine

The antineoplastic effect of bendamustine is due to production of both single- and double-strand breaks The DNA breaks, observed after bendamustine exposure, are more extensive and significantly more durable than those induced by other alkylators. Side effects reported are fever, chills, or itching during or shortly after the injection; low white cell count are reported . signs of tumor cell breakdown such as confusion, weakness, muscle cramps, nausea, vomiting, bradycardia or tachycardia , decreased urination are also observed.

Melphalan, Cyclophosphamide, and Dexamethasone (MCD) as a salvage regimen for heavily treated relapsed or refractory multiple myeloma patients [17]

5. Daratumumab

Is an IgG1κ fully human mAb that targets CD38, a type II transmembrane glycoprotein composed of extracellular, transmembrane, and intracellular domains. Direct effects are mediated by inhibition of intracellular signal transduction, and by inhibition of CD38 enzymatic activity, which leads to decreased levels of immunosuppressive adenosine. Fc-dependent mechanisms include complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), Daratumumab has shown encouraging results both as monotherapy and in combination with other regimens in both Relapsed MM and untreated disease. [18]

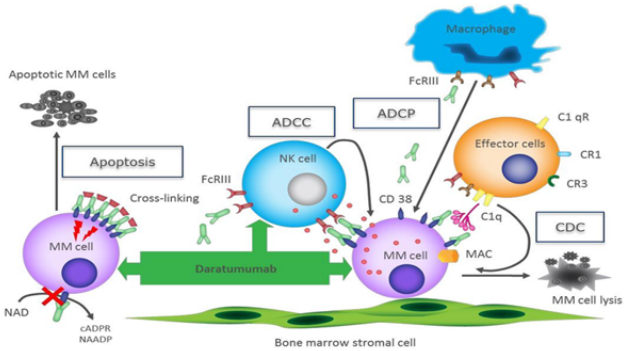

Fig. 7: Daratumumab action

Elotuzumab is a humanized monoclonal antibody used in relapsed multiple myeloma. Elotuzumab directly activates Natural Killer cells through both the SLAMF7 pathway and Fc receptors. Elotuzumab also targets SLAMF7 (Surface antigen CD319 (SLAMF7) is a robust marker of normal plasma cells and malignant plasma cells in multiple myeloma.) and facilitates the interaction with Natural Killer cells to mediate the killing of myeloma cells through antibody-dependent cellular cytotoxicity (ADCC). Useful in relapsed / refractory MM. Elotuzumab, pomalidomide and dexamethasone combination is used in refractory cases. Fatigue, diarrhoea, constipation and cough are commonly observed. [19]

Steroids are commonly used for multiple myeloma treatment and are used at all stages of the disease. In high doses, steroids can lyse multiple myeloma cells. Dexamethasone and the other steroids are useful in myeloma treatment because they can stop white blood cells from traveling to areas where cancerous myeloma cells are causing damage. This decreases the amount of swelling or inflammation in those areas and relieves associated pain and pressure. Dexamethasone inhibits the messenger RNA expression of interleukin-6 (IL-6) in myeloma cells, a growth factor considered to be a major mediator of plasma cell pro1iferation. [21]

Table 5: Comparative trials on multiple myeloma

Trials	**MM03**	**Endeavour**	**Aspire**	**Tourmaline**	**Castor**	**Pollux**	**Eloquent 1**
Overall Response Rate %	31 vs 10	77 vs 63	87 vs 66	78 vs 71	83 vs 63	93 vs 76	79 vs66
Median Progression free survival	3.8 vs 1.9	18.7 vs 9.4	26.3 vs 17.6	20.6 vs 14.7	NR vs 7.2	NA	19.4 vs 14.9
Grade 3/ 4 Adverse events							
Haematological	Neutropenia 48 %	Thrombocytopenia 8 %	Anemia 18%	Neutropenia 22%	Lymphocytopenia 10 %	Anemia 8 %	Anemia 19 %
Non Haematological	Fatigue 5 %	Hypertension 9 %	Hypertension 4%	Diarrhoea 6%	Fatigue 6%	Hypertension 7%	Fatigue 8%
	Prama-lidomide + DXM vs High dose DXM	Carfilzomib + DXM versus Bortezomib + DXM	Carfilzomib + Lenalidomide + DXM vs Lenalidiomide + DXM	Ixazomib + Lenalidomide + DXM Vs Lenalidomide + DXM	Daratumumab + Bortezomib + Dexamethasone vs Bortezomib + Dexamethasone	Daratumumab + Lenalidomide + Dexam-ethasone vs Lanalidomide + Dexam-ethasonme	Elotuzumab + Lenalidomide + Dexamethasone vs Lenalidomide + Dexamethasone

Drugs under evaluation: Many therapeutic drugs are under evaluation for multiple myeloma, mostly in combination with dexamethasone and Proteasome inhibitors.

Table 6: Drugs under investigations

Drug class	Types	Mode	Studies
mTOR inhibitors	Everolimus Temsirolimus	Regulation of cell growth, protein synthesis and cell progression	Phase 1/2, in combination with bortezomib or lenalidomide
MEK1/2 inhibitor	Trametinib	Inhibition of cell growth	Phase 1, in combination with afuresertib in solid tumors and MM
BRAF inhibitor	Vemurafenib	Inhibition of the constitutionally activated NRAS–	Retrospective data in combination in Phase II trials
AKT inhibitor	Afuresertib	Inhibition of cell growth, apoptosis promotion	Advanced hematologic malignancies including MM
anti IL-6	Siltuximab	Promoting cell-apoptosis by blocking IL-6 through a chimeric anti-IL6 monoclonal antibody	Randomized, in combination with bortezomib or placebo
Antibody drug conjugates	Belantamab Lorvotuzumab Milatuzumab	Anti-BCMA (B-cell maturation antigen) Anti-CD56 Anti-CD138	In August 2020, the FDA granted accelerated approval to belantamab mafodotin-blmf as a monotherapy treatment for relapsed or treatment-refractory multiple myeloma.
Alkyl phospholipid inhibitor	Perifosine	Inhibitor of PI3K/Akt and MEK/ERK Pathway	Phase 3 study of perifosine combined with bortezomib and dexamethasone is effective
XPO-1 inhibitor	Selinexor	Selinexor is an oral, potent XPO-1 inhibitor	Combination of selinexor, bortezomib and dexamethasone in patients with less advanced disease. This regimen allowed an ORR of 63%
chimeric antigen receptor T-cell therapy	Orvacabtagene Autoleucel	a B-cell maturation antigen (BCMA)-directed CAR T cell therapy	Patients (pts) with relapsed/refractory multiple myeloma (RRMM)

PVX vaccine is a tri-peptide vaccine for multiple myeloma. This vaccine recognizes three different proteins that are present in on multiple myeloma cells.

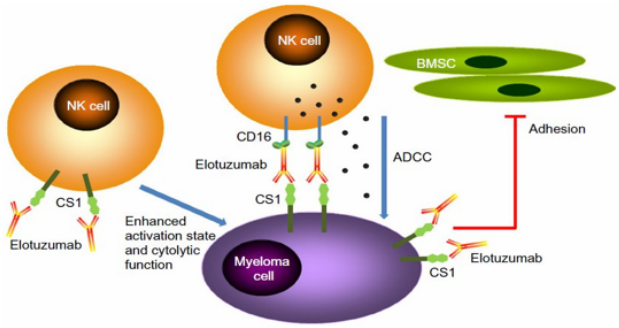

Fig. 8: Elotuzumab action

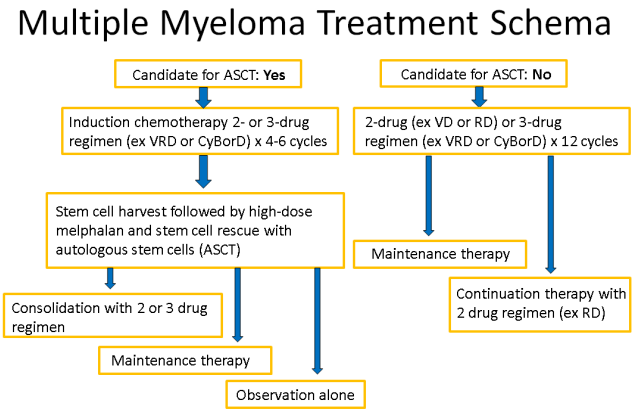

Fig. 9: Algorithm for treating multiple myeloma [20]

6. Drug Combinations in Multiple Myeloma [22]

1. In a prospective study of lenalidomide /bortezomib /dexamethasone in patients with newly diagnosed MM, the rate of partial response (PR) was 100%, with 74% VGPR [very good partial response]or better and 52% complete response (CR) /near CR. The triple-drug regimen group had significantly longer PFS (43 months vs 30 months;) and improved median OS (75 vs 64 months.
2. Bortezomib /Cyclophosphamide /Dexamethasone (70% rates of CR/near CR; rate of at least VGPR or better was 74%.
3. Carfilzomib /Cyclophosphamide /Dexamethasone: The median PFS was 35.7 months in the once-weekly group and 35.5 months in the twice-weekly group, The 3-year OS was 70% and 72%, respectively.
4. ORR after initial therapy with ixazomib /cyclophosphamide /dexamethasone was 73%.
5. The results of the randomized phase III trial by the Spanish Myeloma Group (PETHEMA/GEM) demonstrated a significantly higher CR rate with bortezomib /thalidomide /dexamethasone as primary therapy overall (35% vs 14%, P=.001) and in patients with high-risk cytogenetics (35% vs 0%, P=.002)

ASCT – Autologous Stem Cell Transplant, The combination of bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone, or VRD. VD bortezomib (Velcade), lenalidomide, or RD lenalidomide (Revlimid), and dexamethasone RD regimens, Cyclophosphamide, bortezomib and dexamethasone (CyBorD) induction for newly diagnosed multiple myeloma.

6.1. Indications of radiation therapy [23]

RT remains is a therapeutic component for the management in 34% of patients, and it effectively provides pain relief. RT aims in reducing bone pain**,** spinal cord compression with the involvement of cranial nerves RT has a palliative role in MM, and produces cure in solitary plasmacytomas.

7. Conclusion

MM is a neoplasm of clonal plasma cells which originate from the post-germinal lymphoid B-cell lineage which accounts for 1.8% of all malignancies and 10–15% of hematologic malignancies. MM induction therapy consisted of corticosteroids alone, melphalan/prednisone, or the combination of vincristine, doxorubicin, and dexamethasone (VAD), with a median survival of 2- 3 years. The introduction of proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and monoclonal antibodies (MABs) have improved treatment outcomes and extended the median OS to over 15 years in some individuals. Daratumumab, Elotuzumab have shown encouraging results both as monotherapy and in combination with other regimens in both Relapsed multiple myeloma and Untreated disease.

ASCT is not curative in MM, but improves median OS by 12 months. The treatment-related mortality rate is 1–2%. In ~50% of patients, Autologous stem cell transplantation can be done on an outpatient basis. One of the most common complications of symptomatic MM is renal impairment affecting 20–30% of patients at the time of diagnosis and around 10% of them require haemodialysis, with a negative impact on prognosis.

8. Source of Funding

None.

9. Conflict of Interest

None.

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