Annals of Hematology (2019) 98:19–28
https://doi.org/10.1007/s00277-018-3465-8

REVIEW ARTICLE

Glucocorticoids in multiple myeloma: past, present, and future

Nicholas Burwick[1,2] · Sanjai Sharma[3]

Received: 19 March 2018 / Accepted: 26 July 2018 / Published online: 2 August 2018
© This is a U.S. Government work and not under copyright protection in the US; foreign copyright protection may apply 2018

Abstract
Glucocorticoids are a backbone of treatment for multiple myeloma in both the upfront and relapsed/refractory setting. While glucocorticoids have single agent activity in multiple myeloma, in the modern era, they are paired with novel agents to induce high clinical response rates. On the other hand, toxicities of steroid therapy limit high dose delivery and impact patient quality of life. We provide a history of steroid use in multiple myeloma with the aim to understand how steroids have emerged and persisted in the treatment of multiple myeloma. We review mechanisms of glucocorticoid sensitivity and resistance and highlight potential future directions to evaluate steroid responsiveness. Further research in this area will aid in optimizing steroid utilization and help determine when glucocorticoid therapy may no longer benefit patients.

Keywords Multiple myeloma · Glucocorticoids · Dexamethasone · Apoptosis · Drug resistance

Introduction

Glucocorticoids (GCs) such as prednisone and dexamethasone are steroid hormones that have been used to treat multiple myeloma, a plasma cell cancer, for over 50 years. It is known that GCs bind cytosolic glucocorticoid receptors (GRs) which then translocate to the nucleus to modulate gene expression. The GC-GR complex binds as a homodimer to GC response elements to transactivate target genes including annexin I and MAPK phosphatase 1 [1]. In addition, glucocorticoids indirectly repress target genes via inhibitory interactions of GC-GR monomers with transcription factors including nuclear factor κB and activator protein-1 (AP-1) [2], important factors in multiple myeloma pathogenesis [3–5]. The net effect is the promotion of broad anti-inflammatory and immunosuppressive activity. In addition, glucocorticoids promote gluconeogenesis, glycogenolysis, and lipolysis [6] and induce catabolic effects in skeletal muscle [7]. Thus, the potent action of glucocorticoids in multiple myeloma must be weighed against potential toxicities for the patient [8, 9].

✉ Nicholas Burwick
nburwick@u.washington.edu

[1] VA Puget Sound Health Care System, Seattle, WA, USA

[2] Department of Medicine, University of Washington, 1705 NE Pacific St, M/S 358280, Seattle, WA 98195, USA

[3] Sequoia Regional Cancer Center, Visalia, CA, USA

Clinical background

Glucocorticoids arrive on the scene

In 1962, the Western Cancer Oncology Group performed a randomized double-blind study of prednisone (40 mg daily) versus placebo in 65 patients with multiple myeloma. While patients treated with prednisone had significant decreases in hematocrit and globulin levels, there was no significant difference in survival compared to placebo [10]. Subsequently, in 1969, Alexanian et al. reported on pivotal experience treating multiple myeloma patients with either melphalan alone or melphalan combined with prednisone using different dosing strategies [11]. The addition of prednisone to melphalan clearly improved response rates and overall survival. Subsequent reports in the 1980s demonstrated that multiple myeloma patients resistant to alkylating agents could be effectively salvaged with high-dose dexamethasone, a synthetic glucocorticoid, along with infusional vincristine and doxorubicin (VAD) [12].

Single-agent glucocorticoids vs chemotherapy

The promising results with glucocorticoids, and in particular high-dose dexamethasone, raised the question as to whether high-dose steroids were the primary driver of disease responses in multiple myeloma. To help address this question, in 1986, Alexanian et al. reported on the M.D. Anderson

experience on the use of single agent high-dose dexamethasone in multiple myeloma patients, compared to historical controls treated with VAD. While VAD outperformed single agent dexamethasone in those with chemo-sensitive disease, patients with refractory myeloma had similar responses whether they received single agent dexamethasone or chemotherapy [13]. Additional studies confirmed significant response rates with single agent high-dose dexamethasone in the relapsed/refractory setting; however, it was also becoming clear that higher doses of dexamethasone had potential for severe toxicities, including thrombosis, infections, gastrointestinal bleeding, and psychosis [14]. Nonetheless, enthusiasm for single agent high-dose dexamethasone continued, and in 1992, a report on 112 previously untreated myeloma patients demonstrated a response rate of 43%, comparable to prior reports using VAD [15].

As a result of these studies, the utilization of high-dose dexamethasone in the frontline treatment of multiple myeloma was now under way (Table 1).

Balancing risk and benefit in glucocorticoid dosing

In 2006, the Intergroupe Francophone du Myélome group reported on a frontline study in older patients comparing melphalan-prednisone, with dexamethasone-based regimens including single agent dexamethasone ± melphalan. Despite similar partial response rates between melphalan-prednisone vs single agent dexamethasone, toxicity continued to be an issue with high-dose dexamethasone, and thus, melphalan-prednisone became a preferred approach in older patients [17]. While response rates of single agent high-dose dexamethasone in phase III studies is around 40% [16], in the relapsed setting, the response rate is much lower [18].

Perhaps in a final blow to the routine use of high-dose dexamethasone, a study of lenalidomide ± low-dose dexamethasone (40 mg once weekly) vs high-dose dexamethasone demonstrated increased deaths in the high-dose dexamethasone arm. Fatal events appeared primarily drug-related due to excess toxicity rather than disease-related, since response rates were higher with high-dose delivery [19].

While high-dose delivery of dexamethasone may partially overcome disease resistance, lower doses of dexamethasone are often favored.

Scientific background

Glucocorticoid mechanisms of action in multiple myeloma

In 1972, Ghering et al. reported that nanomolar concentrations of dexamethasone induced cytotoxicity in several multiple myeloma cell lines containing cytosolic glucocorticoid receptors. Cytoplasmic binding sites for dexamethasone numbered 6500 per cell and were saturated around 50 nM [20]. There is a strong correlation between induction of glucocorticoid response element transactivation and induction of apoptosis in myeloma cells [21]. Glucocorticoid-mediated transrepression of nuclear factor κB is also sufficient, though not required, to induce apoptosis in MM cells [21]. Dexamethasone treatment leads to upregulation of pro-apoptotic genes, down-regulation of anti-apoptotic genes [22], cleavage of both poly (ADP-ribose) polymerase and caspase 3 [23, 24] and activation of intrinsic apoptotic pathways [25].

Dexamethasone treatment also leads to suppression of protein synthesis via the phosphorylation of eIF2-alpha and induction of REDD1, an inhibitor of mTOR [26]. Moreover, inhibitors of mTOR sensitize multiple myeloma cells to dexamethasone-induced apoptosis, an effect mediated by inhibition of cap-dependent translation [27]. In a study evaluating synthetic lethality with dexamethasone in multiple myeloma, it was found that suppression of all three subunits of eIF4F cap-binding complex synergized with dexamethasone to induce cell death, while eIF4F inhibition attenuated dexamethasone resistance [28] (Fig. 1).

Mechanisms of glucocorticoid resistance in multiple myeloma

By the early 1990s, multiple studies emerged noting a critical role for the cytokine factor interleukin 6 (IL-6) in overcoming dexamethasone sensitivity. For example, it was noted that dexamethasone suppressed IL-6 mRNA gene expression and that dexamethasone-sensitivity could be overcome by excess IL-6 [29–31]. It also became clear that IL-6 paracrine secretion from the tumor micro-environment has a pivotal role in dexamethasone drug resistance in multiple myeloma [32, 33], as does tumor-stromal cell interactions [34]. Additional molecules including insulin-like growth factor and vascular endothelial growth factor, among others, also support myeloma growth [35, 36].

Further mechanisms of dexamethasone resistance have been described including the disruption of pro-apoptotic caspases by over-expression of heat shock protein 27 [37], an effect that can be overcome with proteasome inhibition [38]. The upregulation of JunB, a member of the AP-1 transcription factor family, is also associated with dexamethasone resistance. Dexamethasone sensitivity can be restored via JUNB knockdown, while blockade of IL-6 inhibits stromal cell-mediated upregulation of JunB in myeloma cells [5]. Increased expression of the miRNA cluster miR-221-222 is associated with dexamethasone resistance and is mediated by down-regulation of the p53-upregulated modulator of apoptosis (PUMA) [39].

While there is a report of a glucocorticoid receptor (NR3C1) gene mutation in a patient with multiple myeloma

Table 1 Glucocorticoid single agent activity in multiple myeloma. Response rates to single agent glucocorticoids (prednisone, dexamethasone) in published reports are tabulated, including the number of patients in each report (*n*), the dose per cycle, the percent of partial responses, and prior treatment regimens, with corresponding references

Glucocorticoid	Subjects (*n*)	Dose/cycle	Cycle length	Response rate[a]	Prior treatment	Reference
Prednisone	33	40 mg/day	n/a	28%[b]	Not reported	Mass RE 1962 [10]
Dexamethasone	19	480 mg	5 weeks	21%[c]	Relapsed	Alexanian R 1986 [13]
Dexamethasone	30	480 mg	5 weeks	27%[c]	Unresponsive[d]	Alexanian R 1986 [13]
Dexamethasone	32	160 mg cycle 1–8 160 mg cycle 9-	1 week 2 weeks	40%[e]	77% 1–2 lines	Friedenberg WR 1991 [14]
Dexamethasone[f]	112	240 mg/m^2	5 weeks	43%[c]	New diagnosis	Alexanian R 1992 [15]
Dexamethasone	100	480 mg	4 weeks	41%[e]	New diagnosis	Rajkumar SV 2006 [16]
Dexamethasone	127	480 mg cycle 1–2 160 mg cycle 3–12	6 weeks 6 weeks	40%[e]	New diagnosis	Facon T 2006 [17]
Dexamethasone	336	480 mg cycle 1–4 160 mg cycle 5–9	5 weeks	18%[e]	Median = 2.0 lines	Richardson PG 2005 [18]

n number

[a] Partial response rates

[b] Decrease in globulin by 1.5%

[c] ≥ 75% reduction

[d] < 75% reduction to prior treatment

[e] ≥ 50% reduction

[f] Followed by maintenance interferon

[40], NR3C1 mutations have not been commonly reported in human myeloma specimens [41]. Nonetheless, low-level NR3C1 expression is associated with inferior survival outcomes in multiple myeloma patients compared to those with higher levels [42, 43]. In a human multiple myeloma cell line, resistance to glucocorticoids was found to involve a block to transcriptional elongation within intron B of NR3C1 [44] and is associated with high-level expression of a variant glucocorticoid receptor mRNA whose protein product is predicted to impact hormone binding [45]. Responsiveness of myeloma cells to dexamethasone varies by glucocorticoid receptor (GR) isoform. The GRα isoform is predominant in sensitive cell lines, while the GR-P isoform predominates in resistant myeloma cell lines [46]. In acute lymphoblastic leukemia, a setting in which glucocorticoids are also a backbone treatment [47], low glucocorticoid receptor levels have been found to correlate with poor response to therapy [48]. However, whether glucocorticoid receptor isoforms or receptor abundance patterns correlate with clinical activity in multiple myeloma patients remains unclear.

Whether multiple myeloma cells have or develop intrinsic resistance to glucocorticoids would also be an important aspect of drug selection for patients. Approximately 20% of myeloma patients harbor mutations in genes that dysregulate NF-κB, resulting in constitutive activation, the most common being inactivation of TNF receptor-associated factor 3 (*TRAF3*) [4]. Patients with low levels of *TRAF3* have low response rates to dexamethasone, compared to those with higher *TRAF3* levels [4]. In another study, *NRAS* mutations, which are also present in about 20% of myeloma patients, were associated with low response rates to bortezomib, while 3 of 6 patients with *NRAS* mutations responded to high-dose dexamethasone [49]. Additional recurrent mutations have been described in multiple myeloma patient cells, including in genes involved in RNA processing and protein homeostasis [41], and it is unknown how these mutations might impact glucocorticoid sensitivity. While more data is needed, in the future, gene expression or mutational analysis could help guide decision making regarding continued use of dexamethasone, ideally in the setting of a clinical study.

Overall, this era saw great strides in elucidating the mechanisms of dexamethasone sensitivity and resistance in multiple myeloma (Fig. 2). However, the precise mechanisms of drug resistance in multiple myeloma patients remain to be fully explored.

Present perspectives

Pairing glucocorticoids with novel agents: the new paradigm

In the modern area, significant progress has been made in the discovery of novel agents that pair well with glucocorticoid mechanism of action, to promote synergistic effects. For example, the immunomodulatory drug thalidomide and analogs (IMIDs), in pre-clinical studies, demonstrate that the IMIDs directly augment anti-proliferative effects on myeloma cells in

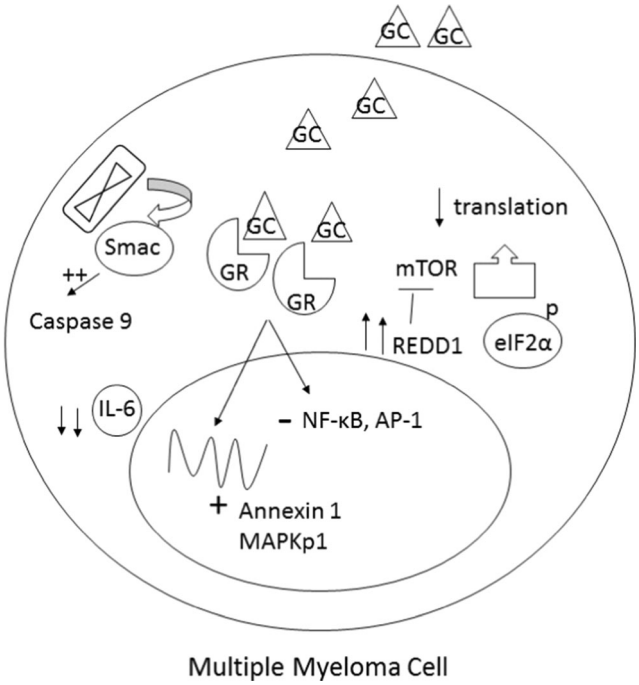

Fig. 1 Glucocorticoid mechanisms of action in multiple myeloma. Glucocorticoids bind cytosolic glucocorticoid receptors which translocate to the nucleus, leading to transactivation and transrepression of target genes. Glucocorticoids inhibit IL-6 production, induce release of Smac from mitochrondria leading to caspase 9 activation, and inhibit mRNA translation via inhibition of mTOR and phosphorylation of eIF2-alpha. GC = glucocorticoid, GR = glucocorticoid receptor, IL-6 = interleukin 6, NF-kB = nuclear factor kB, AP-1 = activator protein-1, MAPKp1 = MAPK phosphatase 1, mTOR = mechanistic target of rapamycin, Smac = second mitochondria-derived activator of caspases

combination with dexamethasone [50]. In part, the additive effects in promoting myeloma apoptosis reflect differences in mechanisms of action, with IMIDs promoting extrinsic apoptosis and dexamethasone promoting intrinsic apoptosis [51]. While exogenous IL-6 can overcome these effects, it is notable that the IMIDs are able to inhibit the production of IL-6 from both myeloma cells and bone marrow stromal cells [52]. Moreover, IMIDs such as thalidomide have been found to reverse the poor prognostic significance associated with low *NR3C1* expression [43].

On the other hand, IMIDs such as lenalidomide cause selective degradation of Ikaros family zinc finger protein 1, whose loss of function has been found to mediate glucocorticoid resistance in acute lymphoblastic leukemia [53, 54]. However, since the overall clinical activity of these agents when used in combination is so high, it remains unclear if this latter mechanism of action impacts drug synergism in a meaningful way when treating multiple myeloma patients.

The proteasome inhibitors such as bortezomib are another group of highly active novel agents that pair well with glucocorticoids. It has been demonstrated that proteasome inhibition overcomes resistance to exogenous IL-6, decreases myeloma cell adherence to bone marrow stromal cells, and decreases bone marrow stromal cell IL-6 secretion, leading to additive apoptotic effects with dexamethasone [55]. Combination treatment of IMIDs, proteasome inhibitors, and glucocorticoids in myeloma patients have confirmed very high clinical response rates when these drugs are used together [56]. Newer proteasome inhibitors, including ixazomib, and carfilzomib, and IMIDs such as pomalidomide, are also

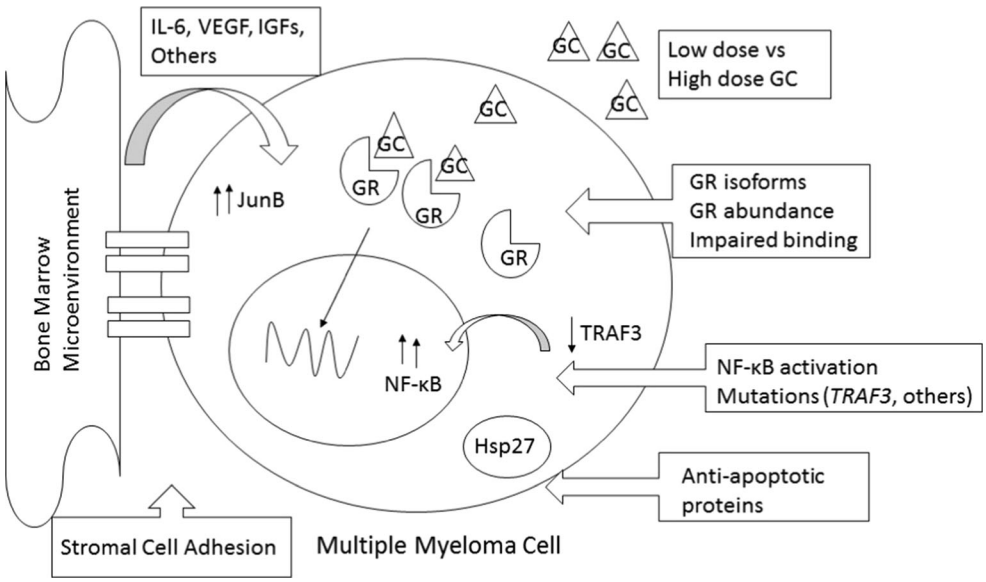

Fig. 2 Mechanisms of resistance to glucocorticoids. Resistance of multiple myeloma to glucocorticoids includes cell-extrinsic and cell-intrinsic factors. Extrinsic factors include stromal cell-mediated adhesion and secretion of factors supportive of myeloma cell growth and survival. Intrinsic factors include over-expression of Hsp27, activation of NF-kB, or glucocorticoid receptor modulation. GC = glucocorticoid, GR = glucocorticoid receptor, IL-6 = interleukin 6, VEGF = vascular endothelial growth factor, IGFs = insulin-like growth factors, Hsp = heat shock protein, NF-kB = nuclear factor kB, AP-1 = activator protein-1, TRAF = TNF receptor-associated factor

commonly paired with dexamethasone in the relapsed/refractory setting [57–60]. Since these drugs have not typically been studied with or without steroids in clinical studies, it remains poorly understood if synergistic mechanisms remain potent after failing a first-line steroid-based regimen.

Selinexor, a selective inhibitor of XPO1-mediated nuclear export, demonstrates synergistic anti-tumor activity with dexamethasone [61]. The glucocorticoid receptor is an XPO1 cargo, and treatment with selinexor thus enhances glucocorticoid receptor transcriptional activation. In support of clinically relevant drug synergism, early phase studies with selinexor alone showed minimal response, while combination with low-dose dexamethasone significantly increased response rates [62]. Moreover, clinical responses have been seen with selinexor and low-dose dexamethasone even in those with relapsed/refractory multiple myeloma having received a median of seven prior lines of treatment [63]. Thus, this is a promising novel drug combination that takes advantage of glucocorticoid drug synergism.

Panobinostat, a histone deacetylase inhibitor, also has activity in multiple myeloma and has demonstrated responses in combination with bortezomib and dexamethasone, as well as in combination with lenalidomide and dexamethasone, among other steroid-containing combinations [64–66]. Potentiation of panobinostat with dexamethasone has been demonstrated in vitro and in murine models, demonstrating a rationale for these clinical combinations [67]. While data is limited on the precise clinical benefit of dexamethasone in this setting, in a phase I study, the addition of dexamethasone to a small expansion cohort appeared to increase response rates compared to panobinostat/bortezomib alone [68]. Thus, there is a rationale to keep glucocorticoids on board when using this combination and is the on-label approach.

Clarithromycin is a macrolide antibiotic which has minimal single agent activity against multiple myeloma [69, 70], but which augments the activity of dexamethasone. Clarithromycin, when used in combination with lenalidomide and dexamethasone, demonstrates high clinical response rates, which appear to be significantly higher when compared to lenalidomide and dexamethasone alone [71, 72]. The ability of clarithromycin to enhance dexamethasone sensitivity may reflect its effects on delaying glucocorticoid clearance and shifting of the dexamethasone dose-response curve to the left [73, 74]. Thus, it is important to pair this agent with a glucocorticoid backbone.

As IL-6 secretion is a major mechanism of resistance to dexamethasone in multiple myeloma, the utility of targeted inhibition of IL-6 has also been evaluated in pre-clinical studies in combination with dexamethasone. Although IL-6 monoclonal antibody appears to have limited single agent activity against myeloma cells, inhibition of IL-6 potentiates dexamethasone-mediated apoptosis and attenuates bone marrow stromal cell-mediated resistance to dexamethasone [75]. Clinical studies of siltuximab, an IL-6 monoclonal antibody, ± high-dose dexamethasone demonstrate that the combination of these drugs, but not siltuximab alone, has modest clinical activity in relapsed/refractory patients [76]. While it is likely that blocking IL-6 has an important role in overcoming dexamethasone resistance, additional resistance mechanisms may need to be overcome, especially in the relapsed/refractory setting.

Elotuzumab, a monoclonal antibody targeting SLAMF7, has also been found to have promising single agent anti-myeloma activity in pre-clinical studies. The activity of elotuzumab involves both promotion of antibody-dependent cellular cytotoxicity and augmentation of natural killer cell anti-tumor effect [77, 78]. A phase I dose-escalation study, while designed to assess safety and tolerability, demonstrated no objective responses to single-agent elotuzumab [79]. Subsequent studies, however, which have largely investigated elotuzumab in combination with lenalidomide and dexamethasone have demonstrated high response rates [80, 81]. Pre-clinical rationale for the combination of elotuzumab and lenalidomide include the ability of lenalidomide to augment anti-myeloma activity via increased natural killer cell activation [82]. Glucocorticoids, in contrast, have been shown to reduce natural killer cell activity [83, 84], which would seem to be antagonistic, in part, to the mechanism of action of these drugs. Nonetheless, as this regimen has typically been used in combination, it is difficult to tease out what the precise impact of dexamethasone is in this setting.

In contrast to the experience with siltuximab and elotuzumab, promising single agent activity has been seen with daratumumab, an anti-CD38 monoclonal antibody in relapsed/refractory patient populations [85]. While dexamethasone was not included in early single agent studies, dexamethasone was added to subsequent trials with daratumumab in combination with lenalidomide or bortezomib with high clinical activity [86, 87]. In contrast, a phase II study of daratumumab and dexamethasone without an IMID or proteasome inhibitor reported a response rate of only 25% [88]. While difficult to compare across studies, this response rate was not higher than that seen with single agent daratumumab [85], so it is difficult to conclude that dexamethasone synergizes with daratumumab in myeloma patients. It should be noted, however, that glucocorticoids have a role as a premedication agent to reduce daratumumab infusion reactions. Overall, given the data from the large phase III POLLUX and CASTOR trials alluded to above, dexamethasone usage will likely continue to be high when using this novel agent. Nonetheless, in the emerging era of immuno-therapeutics, the role of dexamethasone in dampening immune responses will need to be carefully considered.

Overall, in the modern area, dexamethasone-free regimens continue to be the exception, rather than the rule.

Glucocorticoids and adverse toxicities

In addition to glucocorticoid activity in multiple myeloma, increased understanding of glucocorticoid effects in other tissues has provided insight into glucocorticoid toxicity. In skeletal muscle for example, where glucocorticoids induce muscle atrophy, dexamethasone has been found to rapidly impair peptide chain initiation and inhibit protein synthesis by as much as 50–80% [89–93]. Inhibition of ternary complex formation via eIF2-alpha activation appears to have a role in this response, though results have been variable [91, 93–95]. Dexamethasone also represses mTOR in skeletal muscle via upregulation of REDD1 leading to reduced phosphorylation of down-stream targets S6K1 and 4E-BP1 [96]. Since dexamethasone also suppresses protein synthesis in multiple myeloma cells by similar actions, more work is needed to determine if glucocorticoid-induced muscle atrophy can be teased out from its anti-myeloma effects.

It has also been appreciated that many unwanted glucocorticoid side effects likely stem from glucocorticoid transactivation rather than transrepression, including adverse metabolic effects such as those regulating glucose homeostasis [97]. In contrast, the transrepression of transcription factors such as nuclear factor κB and AP-1, which regulate pro-inflammatory cytokines, likely plays a role in glucocorticoid-induced anti-myeloma activity. With this rationale in mind, selective glucocorticoid receptor agonists and modulators (SEGRAMs) are being developed that favor transrepression over transactivation [98–100]. While some of these agents have demonstrated potent anti-myeloma activity, other reports have been conflicting, and the anti-myeloma activity is likely influenced by the co-activator/co-repressor profile of the particular compound being studied [101–103]. Moreover, the net contribution of these agents to glucocorticoid toxicity may be more nuanced than the simplified separation described above. For example, adverse effects of glucocorticoids on bone metabolism may involve both transactivation and transrepression mechanisms [97]. In addition, glucocorticoids have non-genomic mechanisms of action that may contribute to adverse effects [104]. Overall, the study of SEGRAMs, while promising, remains to be fully explored in multiple myeloma.

In contrast to the SEGRAMs, among the glucocorticoid drugs, all act by the same basic mechanism. Variations in toxicity and efficacy likely relate more to the relative potency and dose of the specific drug used. Dexamethasone for example, which is the most commonly used agent, has a relative potency of 6-fold that of prednisone. Although higher doses of glucocorticoids may increase anti-myeloma activity, the toxicity of glucocorticoids is dose-dependent [14, 19]. A complete discussion of the molecular mechanisms of glucocorticoid side effects is beyond the scope of this review, but this topic is further reviewed in [1, 97, 104, 105].

Future considerations for glucocorticoid use in myeloma

In the relapsed/refractory setting, glucocorticoids continue to be highly utilized. In part, this is reflective of the potent clinical activity of these agents, which may persist well past first-line treatment, probably by promoting drug synergism. Selinexor is a good example of this. Nonetheless, it also reflects the reality that glucocorticoids continue to be included in clinical trials of salvage regimens. Thus, it is difficult for caring providers to know when, if ever, to stop these agents. Is it possible that in some circumstances, we are largely inducing catabolic side effects with limited activity against the actual malignant plasma cell? Studies of real-world glucocorticoid prescribing practices, and correlative patient-level symptom assessments, would be helpful to further understand the scope of this issue. In addition, studies of steroid-sparing regimens, particularly in older frail patients, may allow for future non-steroid options for our patients.

The development and testing of glucocorticoid receptor modulators, and the identification of novel drugs that act down-stream of the glucocorticoid receptor, may help us determine whether we can harness the potent anti-myeloma effects of glucocorticoid agents, while minimizing unwanted toxicities. Finally, more work is needed to determine if and how biologic factors, including tumor biomarkers, or information on mutation status, could be used to predict steroid responsiveness.

Conclusion

A better understanding of mechanisms of glucocorticoid sensitivity and resistance in multiple myeloma have helped to identify optimal drug partners to overcome steroid resistance. Very high response rates have been demonstrated when steroids are paired with novel agents in the frontline setting. Nonetheless, further research focused on in vivo resistance mechanisms and drug-responsiveness in multiple myeloma patients will help guide decision-making regarding ongoing need for steroid treatment. The need for further mechanistic work on this old drug continues to demand our attention.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Rhen T, Cidlowski JA (2005) Antiinflammatory action of glucocorticoids—new mechanisms for old drugs. N Engl J Med 353(16):1711–1723

2. Stahn C, Buttgereit F (2008) Genomic and nongenomic effects of glucocorticoids. Nat Clin Pract Rheumatol 4(10):525–533
3. Annunziata CM, Davis RE, Demchenko Y, Bellamy W, Gabrea A, Zhan F, Lenz G, Hanamura I, Wright G, Xiao W, Dave S, Hurt EM, Tan B, Zhao H, Stephens O, Santra M, Williams DR, Dang L, Barlogie B, Shaughnessy JD Jr, Kuehl WM, Staudt LM (2007) Frequent engagement of the classical and alternative NF-kappaB pathways by diverse genetic abnormalities in multiple myeloma. Cancer Cell 12(2):115–130
4. Keats JJ, Fonseca R, Chesi M, Schop R, Baker A, Chng WJ, van Wier S, Tiedemann R, Shi CX, Sebag M, Braggio E, Henry T, Zhu YX, Fogle H, Price-Troska T, Ahmann G, Mancini C, Brents LA, Kumar S, Greipp P, Dispenzieri A, Bryant B, Mulligan G, Bruhn L, Barrett M, Valdez R, Trent J, Stewart AK, Carpten J, Bergsagel PL (2007) Promiscuous mutations activate the noncanonical NF-kappaB pathway in multiple myeloma. Cancer Cell 12(2):131–144
5. Fan F, Bashari MH, Morelli E, Tonon G, Malvestiti S, Vallet S, Jarahian M, Seckinger A, Hose D, Bakiri L, Sun C, Hu Y, Ball CR, Glimm H, Sattler M, Goldschmidt H, Wagner EF, Tassone P, Jaeger D, Podar K (2017) The AP-1 transcription factor JunB is essential for multiple myeloma cell proliferation and drug resistance in the bone marrow microenvironment. Leukemia 31(7):1570–1581
6. Kuo T, McQueen A, Chen TC, Wang JC (2015) Regulation of glucose homeostasis by glucocorticoids. Adv Exp Med Biol 872:99–126
7. Schakman O, Kalista S, Barbe C, Loumaye A, Thissen JP (2013) Glucocorticoid-induced skeletal muscle atrophy. Int J Biochem Cell Biol 45(10):2163–2172
8. Oray M, Abu Samra K, Ebrahimiadib N, Meese H, Foster CS (2016) Long-term side effects of glucocorticoids. Expert Opin Drug Saf 15(4):457–465
9. Waljee AK, Rogers MA, Lin P, Singal AG, Stein JD, Marks RM et al (2017) Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. BMJ 357:j1415
10. MASS RE (1962 February 01) A comparison of the effect of prednisone and a placebo in the treatment of multiple myeloma. Cancer Chemother Rep 16:257–259
11. Alexanian R, Haut A, Khan AU, Lane M, McKelvey EM, Migliore PJ, Stuckey WJ Jr, Wilson HE (1969) Treatment for multiple myeloma. Combination chemotherapy with different melphalan dose regimens. JAMA 208(9):1680–1685
12. Barlogie B, Smith L, Alexanian R (1984) Effective treatment of advanced multiple myeloma refractory to alkylating agents. N Engl J Med 310(21):1353–1356
13. Alexanian R, Barlogie B, Dixon D (1986 July 01) High-dose glucocorticoid treatment of resistant myeloma. Ann Intern Med 105(1):8–11
14. Friedenberg WR, Kyle RA, Knospe WH, Bennett JM, Tsiatis AA, Oken MM (1991) High-dose dexamethasone for refractory or relapsing multiple myeloma. Am J Hematol 36(3):171–175
15. Alexanian R, Dimopoulos MA, Delasalle K, Barlogie B (1992) Primary dexamethasone treatment of multiple myeloma. Blood 80(4):887–890
16. Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR (2006) Eastern Cooperative Oncology Group. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol 24(3):431–436
17. Facon T, Mary JY, Pegourie B, Attal M, Renaud M, Sadoun A et al (2006) Dexamethasone-based regimens versus melphalan-prednisone for elderly multiple myeloma patients ineligible for high-dose therapy. Blood 107(4):1292–1298
18. Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, Harousseau JL, Ben-Yehuda D, Lonial S, Goldschmidt H, Reece D, San-Miguel JF, Bladé J, Boccadoro M, Cavenagh J, Dalton WS, Boral AL, Esseltine DL, Porter JB, Schenkein D, Anderson KC, Assessment of Proteasome Inhibition for Extending Remissions (APEX) Investigators (2005) Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 352(24):2487–2498
19. Rajkumar SV, Jacobus S, Callander NS, Fonseca R, Vesole DH, Williams ME, Abonour R, Siegel DS, Katz M, Greipp PR, Eastern Cooperative Oncology Group (2010) Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol 11(1):29–37
20. Gehring U, Mohit B, Tomkins GM (1972) Glucocorticoid action on hybrid clones derived from cultured myeloma and lymphoma cell lines. Proc Natl Acad Sci U S A 69(11):3124–3127
21. Sharma S, Lichtenstein A (2008) Dexamethasone-induced apoptotic mechanisms in myeloma cells investigated by analysis of mutant glucocorticoid receptors. Blood 112(4):1338–1345
22. Chauhan D, Auclair D, Robinson EK, Hideshima T, Li G, Podar K, Gupta D, Richardson P, Schlossman RL, Krett N, Chen LB, Munshi NC, Anderson KC (2002) Identification of genes regulated by dexamethasone in multiple myeloma cells using oligonucleotide arrays. Oncogene 21(9):1346–1358
23. Chauhan D, Pandey P, Ogata A, Teoh G, Treon S, Urashima M, Kharbanda S, Anderson KC (1997) Dexamethasone induces apoptosis of multiple myeloma cells in a JNK/SAP kinase independent mechanism. Oncogene 15(7):837–843
24. Chauhan D, Pandey P, Ogata A, Teoh G, Krett N, Halgren R, Rosen S, Kufe D, Kharbanda S, Anderson K (1997) Cytochrome c-dependent and -independent induction of apoptosis in multiple myeloma cells. J Biol Chem 272(48):29995–29997
25. Chauhan D, Hideshima T, Rosen S, Reed JC, Kharbanda S, Anderson KC (2001) Apaf-1/cytochrome c-independent and Smac-dependent induction of apoptosis in multiple myeloma (MM) cells. J Biol Chem 276(27):24453–24456
26. Burwick N, Zhang MY, de la Puente P, Azab AK, Hyun TS, Ruiz-Gutierrez M, Sanchez-Bonilla M, Nakamura T, Delrow JJ, MacKay VL, Shimamura A (2017) The eIF2-alpha kinase HRI is a novel therapeutic target in multiple myeloma. Leuk Res 55:23–32
27. Yan H, Frost P, Shi Y, Hoang B, Sharma S, Fisher M, Gera J, Lichtenstein A (2006) Mechanism by which mammalian target of rapamycin inhibitors sensitize multiple myeloma cells to dexamethasone-induced apoptosis. Cancer Res 66(4):2305–2313
28. Robert F, Roman W, Bramoulle A, Fellmann C, Roulston A, Shustik C et al (2014) Translation initiation factor eIF4F modifies the dexamethasone response in multiple myeloma. Proc Natl Acad Sci U S A 111(37):13421–13426
29. Ishikawa H, Tanaka H, Iwato K, Tanabe O, Asaoku H, Nobuyoshi M, Yamamoto I, Kawano M, Kuramoto A (1990) Effect of glucocorticoids on the biologic activities of myeloma cells: inhibition of interleukin-1 beta osteoclast activating factor-induced bone resorption. Blood 75(3):715–720
30. Hardin J, MacLeod S, Grigorieva I, Chang R, Barlogie B, Xiao H, Epstein J (1994) Interleukin-6 prevents dexamethasone-induced myeloma cell death. Blood 84(9):3063–3070
31. Lichtenstein A, Tu Y, Fady C, Vescio R, Berenson J (1995) Interleukin-6 inhibits apoptosis of malignant plasma cells. Cell Immunol 162(2):248–255
32. Grigorieva I, Thomas X, Epstein J (1998) The bone marrow stromal environment is a major factor in myeloma cell resistance to dexamethasone. Exp Hematol 26(7):597–603

33. Chauhan D, Uchiyama H, Akbarali Y, Urashima M, Yamamoto K, Libermann TA, Anderson KC (1996) Multiple myeloma cell adhesion-induced interleukin-6 expression in bone marrow stromal cells involves activation of NF-kappa B. Blood 87(3):1104–1112
34. McMillin DW, Negri JM, Mitsiades CS (2013) The role of tumour-stromal interactions in modifying drug response: challenges and opportunities. Nat Rev Drug Discov 12(3):217–228
35. Xu F, Gardner A, Tu Y, Michl P, Prager D, Lichtenstein A (1997) Multiple myeloma cells are protected against dexamethasone-induced apoptosis by insulin-like growth factors. Br J Haematol 97(2):429–440
36. Podar K, Tai YT, Davies FE, Lentzsch S, Sattler M, Hideshima T, Lin BK, Gupta D, Shima Y, Chauhan D, Mitsiades C, Raje N, Richardson P, Anderson KC (2001) Vascular endothelial growth factor triggers signaling cascades mediating multiple myeloma cell growth and migration. Blood 98(2):428–435
37. Chauhan D, Li G, Hideshima T, Podar K, Mitsiades C, Mitsiades N, Catley L, Tai YT, Hayashi T, Shringarpure R, Burger R, Munshi N, Ohtake Y, Saxena S, Anderson KC (2003) Hsp27 inhibits release of mitochondrial protein Smac in multiple myeloma cells and confers dexamethasone resistance. Blood 102(9):3379–3386
38. Chauhan D, Li G, Auclair D, Hideshima T, Podar K, Mitsiades N, Mitsiades C, Chen LB, Munshi N, Saxena S, Anderson KC (2004) 2-Methoxyestardiol and bortezomib/proteasome-inhibitor overcome dexamethasone-resistance in multiple myeloma cells by modulating heat shock protein-27. Apoptosis 9(2):149–155
39. Zhao JJ, Chu ZB, Hu Y, Lin J, Wang Z, Jiang M, Chen M, Wang X, Kang Y, Zhou Y, Chonghaile TN, Johncilla ME, Tai YT, Cheng JQ, Letai A, Munshi NC, Anderson KC, Carrasco RD (2015) Targeting the miR-221-222/PUMA/BAK/BAX pathway abrogates dexamethasone resistance in multiple myeloma. Cancer Res 75(20):4384–4397
40. Egan JB, Kortuem KM, Kurdoglu A, Izatt T, Aldrich J, Reiman R, Phillips L, Baker A, Shi CX, Schmidt J, Liang WS, Craig DW, Carpten JD, Stewart AK (2013) Extramedullary myeloma whole genome sequencing reveals novel mutations in Cereblon, proteasome subunit G2 and the glucocorticoid receptor in multi drug resistant disease. Br J Haematol 161(5):748–751
41. Chapman MA, Lawrence MS, Keats JJ, Cibulskis K, Sougnez C, Schinzel AC, Harview CL, Brunet JP, Ahmann GJ, Adli M, Anderson KC, Ardlie KG, Auclair D, Baker A, Bergsagel PL, Bernstein BE, Drier Y, Fonseca R, Gabriel SB, Hofmeister CC, Jagannath S, Jakubowiak AJ, Krishnan A, Levy J, Liefeld T, Lonial S, Mahan S, Mfuko B, Monti S, Perkins LM, Onofrio R, Pugh TJ, Rajkumar SV, Ramos AH, Siegel DS, Sivachenko A, Stewart AK, Trudel S, Vij R, Voet D, Winckler W, Zimmerman T, Carpten J, Trent J, Hahn WC, Garraway LA, Meyerson M, Lander ES, Getz G, Golub TR (2011) Initial genome sequencing and analysis of multiple myeloma. Nature 471(7339):467–472
42. van Rhee F, Szymonifka J, Anaissie E, Nair B, Waheed S, Alsayed Y, Petty N, Shaughnessy JD, Hoering A, Crowley J, Barlogie B (2010) Total therapy 3 for multiple myeloma: prognostic implications of cumulative dosing and premature discontinuation of VTD maintenance components, bortezomib, thalidomide, and dexamethasone, relevant to all phases of therapy. Blood 116(8):1220–1227
43. Heuck CJ, Szymonifka J, Hansen E, Shaughnessy JD, Usmani SZ, van Rhee F, Anaissie E, Nair B, Waheed S, Alsayed Y, Petty N, Bailey C, Epstein J, Hoering A, Crowley J, Barlogie B (2012) Thalidomide in total therapy 2 overcomes inferior prognosis of myeloma with low expression of the glucocorticoid receptor gene NR3C1. Clin Cancer Res 18(19):5499–5506
44. Sanchez-Vega B, Gandhi V (2009) Glucocorticoid resistance in a multiple myeloma cell line is regulated by a transcription elongation block in the glucocorticoid receptor gene (NR3C1). Br J Haematol 144(6):856–864
45. Moalli PA, Pillay S, Weiner D, Leikin R, Rosen ST (1992) A mechanism of resistance to glucocorticoids in multiple myeloma: transient expression of a truncated glucocorticoid receptor mRNA. Blood 79(1):213–222
46. Sanchez-Vega B, Krett N, Rosen ST, Gandhi V (2006) Glucocorticoid receptor transcriptional isoforms and resistance in multiple myeloma cells. Mol Cancer Ther 5(12):3062–3070
47. Tissing WJ, Meijerink JP, den Boer ML, Pieters R (2003) Molecular determinants of glucocorticoid sensitivity and resistance in acute lymphoblastic leukemia. Leukemia 17(1):17–25
48. Bloomfield CD, Smith KA, Peterson BA, Munck A (1981) Glucocorticoid receptors in adult acute lymphoblastic leukemia. Cancer Res 41(11 Pt 2):4857–4860
49. Mulligan G, Lichter DI, Di Bacco A, Blakemore SJ, Berger A, Koenig E et al (2014) Mutation of NRAS but not KRAS significantly reduces myeloma sensitivity to single-agent bortezomib therapy. Blood 123(5):632–639
50. Hideshima T, Chauhan D, Shima Y, Raje N, Davies FE, Tai YT, Treon SP, Lin B, Schlossman RL, Richardson P, Muller G, Stirling DI, Anderson KC (2000) Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. Blood 96(9):2943–2950
51. Mitsiades N, Mitsiades CS, Poulaki V, Chauhan D, Richardson PG, Hideshima T, Munshi NC, Treon SP, Anderson KC (2002) Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications. Blood 99(12):4525–4530
52. Gupta D, Treon SP, Shima Y, Hideshima T, Podar K, Tai YT, Lin B, Lentzsch S, Davies FE, Chauhan D, Schlossman RL, Richardson P, Ralph P, Wu L, Payvandi F, Muller G, Stirling DI, Anderson KC (2001) Adherence of multiple myeloma cells to bone marrow stromal cells upregulates vascular endothelial growth factor secretion: therapeutic applications. Leukemia 15(12):1950–1961
53. Kronke J, Udeshi ND, Narla A, Grauman P, Hurst SN, McConkey M, Svinkina T, Heckl D, Comer E, Li X, Ciarlo C, Hartman E, Munshi N, Schenone M, Schreiber SL, Carr SA, Ebert BL (2014) Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells. Science 343(6168):301–305
54. Marke R, Havinga J, Cloos J, Demkes M, Poelmans G, Yuniati L, van Ingen Schenau D, Sonneveld E, Waanders E, Pieters R, Kuiper RP, Hoogerbrugge PM, Kaspers GJL, van Leeuwen FN, Scheijen B (2016) Tumor suppressor IKZF1 mediates glucocorticoid resistance in B-cell precursor acute lymphoblastic leukemia. Leukemia 30(7):1599–1603
55. Hideshima T, Richardson P, Chauhan D, Palombella VJ, Elliott PJ, Adams J, Anderson KC (2001) The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. Cancer Res 61(7):3071–3076
56. Richardson PG, Weller E, Lonial S, Jakubowiak AJ, Jagannath S, Raje NS, Avigan DE, Xie W, Ghobrial IM, Schlossman RL, Mazumder A, Munshi NC, Vesole DH, Joyce R, Kaufman JL, Doss D, Warren DL, Lunde LE, Kaster S, DeLaney C, Hideshima T, Mitsiades CS, Knight R, Esseltine DL, Anderson KC (2010) Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood 116(5):679–686
57. Moreau P, Masszi T, Grzasko N, Bahlis NJ, Hansson M, Pour L, Sandhu I, Ganly P, Baker BW, Jackson SR, Stoppa AM, Simpson DR, Gimsing P, Palumbo A, Garderet L, Cavo M, Kumar S, Touzeau C, Buadi FK, Laubach JP, Berg DT, Lin J, di Bacco A, Hui AM, van de Velde H, Richardson PG, TOURMALINE-MM1 Study Group (2016) Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 374(17):1621–1634

58. San Miguel J, Weisel K, Moreau P, Lacy M, Song K, Delforge M et al (2013) Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol 14(11):1055–1066
59. Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Spicka I, Oriol A et al (2015) Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med 372(2):142–152
60. Chng WJ, Goldschmidt H, Dimopoulos MA, Moreau P, Joshua D, Palumbo A, Facon T, Ludwig H, Pour L, Niesvizky R, Oriol A, Rosiñol L, Suvorov A, Gaidano G, Pika T, Weisel K, Goranova-Marinova V, Gillenwater HH, Mohamed N, Feng S, Aggarwal S, Hájek R (2017) Carfilzomib-dexamethasone vs bortezomib-dexamethasone in relapsed or refractory multiple myeloma by cytogenetic risk in the phase 3 study ENDEAVOR. Leukemia 31(6):1368–1374
61. Kashyap T, Klebanov B, Lee MS, Landesman Y (2015) Selinexor, a selective inhibitor of nuclear export (SINE) compound, shows synergistic anti-tumor activity in combination with dexamethasone characterized by specific pattern of gene expression in multiple myeloma (MM). Blood (126:3683)
62. Chen C, Siegel D, Gutierrez M, Jacoby M, Hofmeister CC, Gabrail N, Baz R, Mau-Sorensen M, Berdeja JG, Savona M, Savoie L, Trudel S, Areethamsirikul N, Unger TJ, Rashal T, Hanke T, Kauffman M, Shacham S, Reece D (2018) Safety and efficacy of selinexor in relapsed or refractory multiple myeloma and Waldenstrom macroglobulinemia. Blood 131(8):855–863
63. Vogl DT, Dingli D, Cornell RF, Huff CA, Jagannath S, Bhutani D, Zonder J, Baz R, Nooka A, Richter J, Cole C, Vij R, Jakubowiak A, Abonour R, Schiller G, Parker TL, Costa LJ, Kaminetzky D, Hoffman JE, Yee AJ, Chari A, Siegel D, Fonseca R, van Wier S, Ahmann G, Lopez I, Kauffman M, Shacham S, Saint-Martin JR, Picklesimer CD, Choe-Juliak C, Stewart AK (2018) Selective inhibition of nuclear export with oral selinexor for treatment of relapsed or refractory multiple myeloma. J Clin Oncol 36(9): 859–866
64. San-Miguel JF, Hungria VT, Yoon SS, Beksac M, Dimopoulos MA, Elghandour A et al (2014, 15) Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol (11):1195–1206
65. Chari A, Cho HJ, Dhadwal A, Morgan G, La L, Zarychta K et al (2017) A phase 2 study of panobinostat with lenalidomide and weekly dexamethasone in myeloma. Blood Adv 1(19):1575–1583
66. Popat R, Brown SR, Flanagan L, Hall A, Gregory W, Kishore B et al (2016) Bortezomib, thalidomide, dexamethasone, and panobinostat for patients with relapsed multiple myeloma (MUK-six): a multicentre, open-label, phase 1/2 trial. Lancet Haematol 3(12):e580
67. Ocio EM, Vilanova D, Atadja P, Maiso P, Crusoe E, Fernandez-Lazaro D, Garayoa M, San-Segundo L, Hernandez-Iglesias T, de Alava E, Shao W, Yao YM, Pandiella A, San-Miguel JF (2010) In vitro and in vivo rationale for the triple combination of panobinostat (LBH589) and dexamethasone with either bortezomib or lenalidomide in multiple myeloma. Haematologica 95(5):794–803
68. San-Miguel JF, Richardson PG, Gunther A, Sezer O, Siegel D, Blade J et al (2013) Phase Ib study of panobinostat and bortezomib in relapsed or relapsed and refractory multiple myeloma. J Clin Oncol 31(29):3696–3703
69. Morris TC, Ranaghan L, Morrison J (2001) Northern Ireland Regional Haematology Group. Phase II trial of clarithromycin and pamidronate therapy in myeloma. Med Oncol 18(1):79–84
70. Musto P, Falcone A, Sanpaolo G, Bodenizza C, Carotenuto M, Carella AM (2002) Inefficacy of clarithromycin in advanced multiple myeloma: a definitive report. Haematologica 87(6):658–659
71. Rossi A, Mark T, Jayabalan D, Christos P, Zafar F, Pekle K, Pearse R, Chen-Kiang S, Coleman M, Niesvizky R (2013) BiRd (clarithromycin, lenalidomide, dexamethasone): an update on long-term lenalidomide therapy in previously untreated patients with multiple myeloma. Blood 121(11):1982–1985
72. Gay F, Rajkumar SV, Coleman M, Kumar S, Mark T, Dispenzieri A, Pearse R, Gertz MA, Leonard J, Lacy MQ, Chen-Kiang S, Roy V, Jayabalan DS, Lust JA, Witzig TE, Fonseca R, Kyle RA, Greipp PR, Stewart AK, Niesvizky R (2010) Clarithromycin (Biaxin)-lenalidomide-low-dose dexamethasone (BiRd) versus lenalidomide-low-dose dexamethasone (Rd) for newly diagnosed myeloma. Am J Hematol 85(9):664–669
73. Fost DA, Leung DY, Martin RJ, Brown EE, Szefler SJ, Spahn JD (1999) Inhibition of methylprednisolone elimination in the presence of clarithromycin therapy. J Allergy Clin Immunol 103(6): 1031–1035
74. Spahn JD, Fost DA, Covar R, Martin RJ, Brown EE, Szefler SJ, Leung DYM (2001) Clarithromycin potentiates glucocorticoid responsiveness in patients with asthma: results of a pilot study. Ann Allergy Asthma Immunol 87(6):501–505
75. Voorhees PM, Chen Q, Small GW, Kuhn DJ, Hunsucker SA, Nemeth JA, Orlowski RZ (2009) Targeted inhibition of interleukin-6 with CNTO 328 sensitizes pre-clinical models of multiple myeloma to dexamethasone-mediated cell death. Br J Haematol 145(4):481–490
76. Voorhees PM, Manges RF, Sonneveld P, Jagannath S, Somlo G, Krishnan A, Lentzsch S, Frank RC, Zweegman S, Wijermans PW, Orlowski RZ, Kranenburg B, Hall B, Casneuf T, Qin X, van de Velde H, Xie H, Thomas SK (2013) A phase 2 multicentre study of siltuximab, an anti-interleukin-6 monoclonal antibody, in patients with relapsed or refractory multiple myeloma. Br J Haematol 161(3):357–366
77. Tai YT, Dillon M, Song W, Leiba M, Li XF, Burger P, Lee AI, Podar K, Hideshima T, Rice AG, van Abbema A, Jesaitis L, Caras I, Law D, Weller E, Xie W, Richardson P, Munshi NC, Mathiot C, Avet-Loiseau H, Afar DEH, Anderson KC (2008) Anti-CS1 humanized monoclonal antibody HuLuc63 inhibits myeloma cell adhesion and induces antibody-dependent cellular cytotoxicity in the bone marrow milieu. Blood 112(4):1329–1337
78. Collins SM, Bakan CE, Swartzel GD, Hofmeister CC, Efebera YA, Kwon H, Starling GC, Ciarlariello D, Bhaskar S, Briercheck EL, Hughes T, Yu J, Rice A, Benson DM (2013) Elotuzumab directly enhances NK cell cytotoxicity against myeloma via CS1 ligation: evidence for augmented NK cell function complementing ADCC. Cancer Immunol Immunother 62(12): 1841–1849
79. Zonder JA, Mohrbacher AF, Singhal S, van Rhee F, Bensinger WI, Ding H, Fry J, Afar DEH, Singhal AK (2012) A phase 1, multicenter, open-label, dose escalation study of elotuzumab in patients with advanced multiple myeloma. Blood 120(3):552–559
80. Richardson PG, Jagannath S, Moreau P, Jakubowiak AJ, Raab MS, Facon T et al (2015) Elotuzumab in combination with lenalidomide and dexamethasone in patients with relapsed multiple myeloma: final phase 2 results from the randomised, open-label, phase 1b-2 dose-escalation study. Lancet Haematol 2(12): 516
81. Lonial S, Dimopoulos M, Palumbo A, White D, Grosicki S, Spicka I, Walter-Croneck A, Moreau P, Mateos MV, Magen H, Belch A, Reece D, Beksac M, Spencer A, Oakervee H, Orlowski RZ, Taniwaki M, Röllig C, Einsele H, Wu KL, Singhal A, San-Miguel J, Matsumoto M, Katz J, Bleickardt E, Poulart V, Anderson KC, Richardson P, ELOQUENT-2 Investigators

(2015) Elotuzumab therapy for relapsed or refractory multiple myeloma. N Engl J Med 373(7):621–631
82. Balasa B, Yun R, Belmar NA, Fox M, Chao DT, Robbins MD, Starling GC, Rice AG (2015) Elotuzumab enhances natural killer cell activation and myeloma cell killing through interleukin-2 and TNF-alpha pathways. Cancer Immunol Immunother 64(1):61–73
83. Eddy JL, Krukowski K, Janusek L, Mathews HL (2014) Glucocorticoids regulate natural killer cell function epigenetically. Cell Immunol 290(1):120–130
84. Krukowski K, Eddy J, Kosik KL, Konley T, Janusek LW, Mathews HL (2011) Glucocorticoid dysregulation of natural killer cell function through epigenetic modification. Brain Behav Immun 25(2):239–249
85. Lokhorst HM, Plesner T, Laubach JP, Nahi H, Gimsing P, Hansson M, Minnema MC, Lassen U, Krejcik J, Palumbo A, van de Donk NWCJ, Ahmadi T, Khan I, Uhlar CM, Wang J, Sasser AK, Losic N, Lisby S, Basse L, Brun N, Richardson PG (2015) Targeting CD38 with daratumumab monotherapy in multiple myeloma. N Engl J Med 373(13):1207–1219
86. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, Rabin N, Orlowski RZ, Komarnicki M, Suzuki K, Plesner T, Yoon SS, Ben Yehuda D, Richardson PG, Goldschmidt H, Reece D, Lisby S, Khokhar NZ, O'Rourke L, Chiu C, Qin X, Guckert M, Ahmadi T, Moreau P, POLLUX Investigators (2016) Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 375(14):1319–1331
87. Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, Spicka I, Hungria V, Munder M, Mateos MV, Mark TM, Qi M, Schecter J, Amin H, Qin X, Deraedt W, Ahmadi T, Spencer A, Sonneveld P, CASTOR Investigators (2016) Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med 375(8):754–766
88. Boyle EM, Petillon MO, Herbaux C, Mimouni J, Leleu X, Karlin L, et al. (2016) Daratumumab in combination with dexamethasone in resistant or refractory multiple myeloma: Primary Results of the IFM2014–04 Trial. Blood (128:2138)
89. Southorn BG, Palmer RM, Garlick PJ (1990) Acute effects of corticosterone on tissue protein synthesis and insulin-sensitivity in rats in vivo. Biochem J 272(1):187–191
90. Rannels SR, Jefferson LS (1980 Jun) Effects of glucocorticoids on muscle protein turnover in perfused rat hemicorpus. Am J Phys 238(6):564
91. Rannels SR, Rannels DE, Pegg AE, Jefferson LS (1978) Glucocorticoid effects on peptide-chain initiation in skeletal muscle and heart. Am J Phys 235(2):134
92. Bullock GR, Carter EE, Elliott P, Peters RF, Simpson P, White AM (1972) Relative changes in the function of muscle ribosomes and mitochondria during the early phase of steroid-induced catabolism. Biochem J 127(5):881–892
93. Shah OJ, Anthony JC, Kimball SR, Jefferson LS (2000) Glucocorticoids oppose translational control by leucine in skeletal muscle. Am J Physiol Endocrinol Metab 279(5):1185
94. Rannels DE, Rannels SR, Li JB, Pegg AE, Morgan HE, Jefferson LS (1980) Effects of glucocorticoids on peptide chain initiation in heart and skeletal muscle. Adv Myocardiol 1:493–501
95. Liu Z, Li G, Kimball SR, Jahn LA, Barrett EJ (2004) Glucocorticoids modulate amino acid-induced translation initiation in human skeletal muscle. Am J Physiol Endocrinol Metab 287(2):275
96. Wang H, Kubica N, Ellisen LW, Jefferson LS, Kimball SR (2006) Dexamethasone represses signaling through the mammalian target of rapamycin in muscle cells by enhancing expression of REDD1. J Biol Chem 281(51):39128–39134
97. Schacke H, Docke WD, Asadullah K (2002) Mechanisms involved in the side effects of glucocorticoids. Pharmacol Ther 96(1):23–43
98. Sundahl N, Bridelance J, Libert C, De Bosscher K, Beck IM (2015) Selective glucocorticoid receptor modulation: new directions with non-steroidal scaffolds. Pharmacol Ther 152:28–41
99. Schacke H, Schottelius A, Docke WD, Strehlke P, Jaroch S, Schmees N, Rehwinkel H, Hennekes H, Asadullah K (2004) Dissociation of transactivation from transrepression by a selective glucocorticoid receptor agonist leads to separation of therapeutic effects from side effects. Proc Natl Acad Sci U S A 101(1):227–232
100. De Bosscher K (2010) Selective glucocorticoid receptor modulators. J Steroid Biochem Mol Biol 120(2–3):96–104
101. Hudson AR, Roach SL, Higuchi RI, Phillips DP, Bissonnette RP, Lamph WW, Yen J, Li Y, Adams ME, Valdez LJ, Vassar A, Cuervo C, Kallel EA, Gharbaoui CJ, Mais DE, Miner JN, Marschke KB, Rungta D, Negro-Vilar A, Zhi L (2007) Synthesis and characterization of nonsteroidal glucocorticoid receptor modulators for multiple myeloma. J Med Chem 50(19):4699–4709
102. Clarisse D, Van Wesemael K, Tavernier J, Offner F, Beck IM, De Bosscher K (2018) Effect of combining glucocorticoids with compound A on glucocorticoid receptor responsiveness in lymphoid malignancies. PLoS One 13(5):e0197000
103. Lesovaya E, Yemelyanov A, Kirsanov K, Popa A, Belitsky G, Yakubovskaya M, Gordon LI, Rosen ST, Budunova I (2013) Combination of a selective activator of the glucocorticoid receptor compound A with a proteasome inhibitor as a novel strategy for chemotherapy of hematologic malignancies. Cell Cycle 12(1):133–144
104. Stahn C, Lowenberg M, Hommes DW, Buttgereit F (2007) Molecular mechanisms of glucocorticoid action and selective glucocorticoid receptor agonists. Mol Cell Endocrinol 275(1–2):71–78
105. Harris E, Tiganescu A, Tubeuf S, Mackie SL (2015) The prediction and monitoring of toxicity associated with long-term systemic glucocorticoid therapy. Curr Rheumatol Rep 17(6):4