



A narrative review of the role of glucocorticoid receptors in prostate cancer: developments in last 5 years

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Background and Objective: Glucocorticoids, secreted from the adrenal gland, are commonly used in the treatment of castration-resistant prostate cancer (CRPC) because of their anti-inflammatory and anti-toxic effects. However, glucocorticoids have been reported to have the opposite effects within the course of treatment. Many studies have shown that glucocorticoid receptors (GRs) are involved in the establishment of a dominant population of androgen-independent malignant cells, which may result in CRPC. In this review, we summarized the mechanisms of GRs in CRPC and the clinical application of glucocorticoids based on the present evidence.

Methods: We summarized the isoforms of GRs and the mechanisms involved in CRPC. An updated literature search was performed from the ClinicalTrials database, the National Center for Biotechnology Information database and European Union Drug Regulating Authorities Clinical Trials database. The focus was on the timeframe from 2017 to 2022. At least one primary or secondary outcome [prostate-specific antigen (PSA) response rate, progression-free survival (PFS) or overall survival (OS) and median time to PSA progression] according to studies should be included.

Key Content and Findings: The molecular structures and applications of the isoforms of GR have been intensively researched in the past 60 years. In recent years, researchers have pointed out that GRs may be involved in the development of CRPC via genomic and non-genomic effects. Clinical trials in the past 5 years have focused on the efficacy of drugs regarding CRPC. The use of glucocorticoids during treatments of CRPC follows the guidelines (e.g., NCCN Guidelines[®], guidelines of CSCO, etc.). Based on the collected data, prednisone appears to be the most widely used steroid hormone, followed by dexamethasone. Comparisons of the PSA response rate and the median time to PSA progression revealed that the efficacy of the 2 hormones is similar; however, further research on the effect of steroid hormone in CRPC is still required.

Conclusions: Various GR isoforms may play an important part in the development of CRPC, whose mechanism remains unclear. Most clinical trials have focused on the use of prednisone in the last 5 years. The efficacy of prednisone and dexamethasone is similar.

Keywords: Castration-resistant prostate cancer (CRPC); glucocorticoids; glucocorticoid receptor (GR); clinical trials

Submitted Jun 24, 2022. Accepted for publication Aug 15, 2022.

doi: 10.21037/tau-22-501

View this article at: <https://dx.doi.org/10.21037/tau-22-501>

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Introduction

Prostate cancer is one of the 10 most common cancers globally and poses a great threat to human health. In men, it is the most frequently diagnosed cancer in 112 countries in 2020 (1). Androgen deprivation therapy is a systemic basic therapy for patients with advanced prostate cancer, and the basis of novel combination therapy. However, despite a median of 18–24 months of treatment, most patients will experience cancer progression into castration-resistant prostate cancer (CRPC) (2-4). The mechanisms involved in the development of CRPC are complex (5). Most studies have focused on androgen receptor (AR)-dependent mechanisms.

Studies based on whole-genome and targeted deoxyribonucleic acid (DNA)-sequencing technologies have shown that the AR genes are the most frequently rearranged genes in CRPC tumors, which promote the expression of AR-variants genes. Li *et al.* [2020] examined ribonucleic acid (RNA)-sequencing data from a cohort of 101 prostate cancer patients and pointed out the enhanced effect of tumor metastasis and the resistance of enzalutamide due to expression of a novel AR-variants gene, and found that AR expression was higher in the experimental group than other groups (6). On the other hand, some researchers also found that the upregulation of AR-variants 7 is associated with development of CRPC (7-9).

AR-independent pathways are considered another factor involved in the development of CRPC. Shorning *et al.* [2020] summarized the new mechanisms of development of CRPC based on the interplay between the *PI3K-AKT-mTOR* pathway and several key oncogenic signaling nodes (10). The expression of microRNAs (11,12) and defects in DNA damage repair (13,14) in CRPC have yet to be researched.

Recently, some researchers noted that glucocorticoid receptors (GRs) are involved (15-17) in the development of CRPC based on emerging evidence that the use of glucocorticoids may contribute to tumor progression in CRPC (18-20). Glucocorticoids are widely used for prostate cancer therapies. They are not only used to arrest the growth and slow the proliferation of tumor cells, they are also effectively used to alleviate symptoms caused by the treatment and tumors (21). However, the mechanisms of their actions on prostate cancer cells remain unclear. Research has shown that GR activation promotes cell proliferation by inhibiting apoptosis, which may confer resistance to anti-androgens (22,23). In this article, we summarized the published data and new ideas on the

effectiveness of steroid hormones and glucocorticoid receptors in CRPC in the past five years based on another paper (24). We present the following article in accordance with the Narrative Review reporting checklist (available at <https://tau.amegroups.com/article/view/10.21037/tau-22-501/rc>).

Methods

We summarized the isoforms of GRs and the mechanisms involved in CRPC. An updated literature search was performed on the effectiveness of steroid hormones used in CRPC from the ClinicalTrials database (<https://clinicaltrials.gov/>), the National Center for Biotechnology Information database (<https://www.ncbi.nlm.nih.gov/>) and European Union Drug Regulating Authorities Clinical Trials database (<https://eudract.ema.europa.eu/>). The focus was on the timeframe from 2017 to 2022. The general terms searched were “glucocorticoids” [Mesh] AND “prostate cancer” in NCBI database, “prostate cancer” and “glucocorticoids” in ClinicalTrials database and EudraCT database. More specific search criteria were then used: Prednisolone/Prednisone/Dexamethasone AND “prostate cancer”/“CRPC”/“castration-resistant prostate cancer”. The status should be completed or trials with results. At least one primary or secondary outcome [prostate-specific antigen (PSA) response rate, progression-free survival (PFS) or overall survival (OS) and median time to PSA progression] according to studies should be included (See [Table 1](#) and [Table S1](#)).

GR

Nuclear receptor superfamily 3, group C, member 1 (*NR3C1*) encodes GRs, is located on chromosome 5 (region 5q31.3) (25), and consists of 9 exons. The alternative splicing and translation of exons has mainly produced 2 isoforms of the *NR3C1* gene (i.e., human GR α and human GR β) (26,27). The classic receptor human GR α has 3 major different functional domains: the N-terminal or immunogenic domain, the DNA-binding domain, and the ligand-binding domain (LBD) ([Figure 1](#)) (28,29). GR α can bind to agonist ligands, and thus dissociate from the heat shock proteins and subsequently regulate target gene expression through the glucocorticoid-responsive elements (GREs) (28). Recently, a study showed that lung cancer metastasis-related protein 1 promotes the transference from advanced metastatic prostate cancer to CRPC by activating

Table 1 The search strategy summary

| Items | Specification |
|---|--|
| Date of search (specified to date, month, and year) | 2022.06.01 |
| Databases and other sources searched | Clinical Trials database (https://clinicaltrials.gov/), the National Center for Biotechnology Information database and European Union Drug Regulating Authorities Clinical Trials database |
| Search terms used (including MeSH and free text search terms and filters) | Search terms: “glucocorticoids” [MeSH] AND “prostate cancer” in NCBI database, “prostate cancer” and “glucocorticoids” in ClinicalTrials database and EudraCT database. More specific search criteria were then used: Prednisolone AND “prostate cancer”/Prednisone AND “prostate cancer”/Dexamethasone AND “prostate cancer” or AND “CRPC” or AND “castration-resistant prostate cancer” Filters: Status: Completed or Trials with results |
| Timeframe | 2015.03–2022.01 |
| Inclusion and exclusion criteria (study type, language restrictions, etc.) | Selection criteria: (I) results include PSA response rate, PFS or OS, median time to PSA progression as part of a study (at least one primary or secondary outcome according to studies); (II) mainly focus on the effectiveness of glucocorticoids; (III) ≥15 patients participated in studies |
| Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.) | Studies selected by Zhou and Shi independently. Then studies were integrated |
| Any additional considerations, if applicable | N/A |

CRPC, castration-resistant prostate cancer; PSA, prostate-specific antigen; PFS, progression-free survival; OS, overall survival; N/A, not applicable.

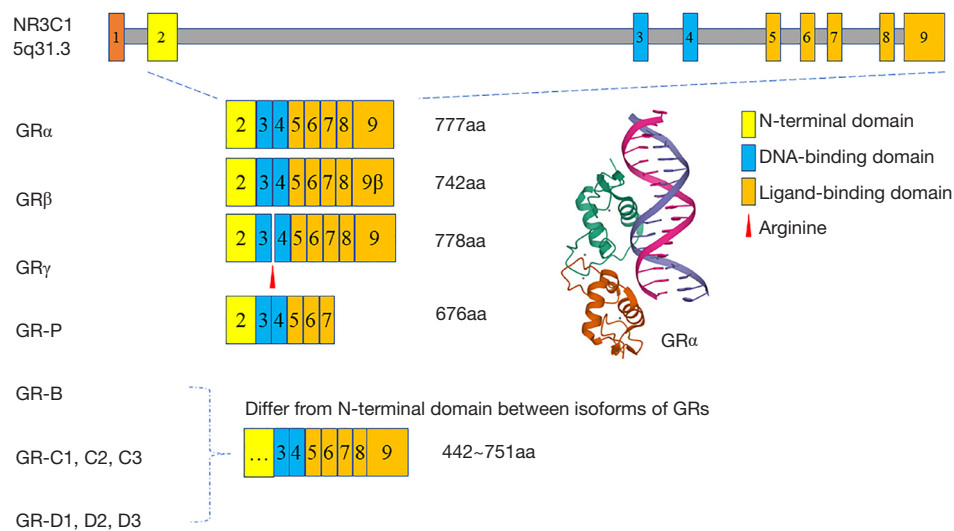


Figure 1 Isoforms of GRs. NR3C1 consists of 9 exons. Exon 2 encodes the N-terminal domain. Exons 3 and 4 encode the DNA-binding domain. Exons 5–9 encode the hinge region and ligand-binding domain. NR3C1, nuclear receptor superfamily 3, group C, member 1; GR, glucocorticoid receptor; DNA, deoxyribonucleic acid.

the GR α signaling pathway (30).

Another isoform of GR, named human GR β , whose LBD is different than that of GR α , does not conventionally bind to glucocorticoid agonists. Recent researches revealed that GR β is localized both in the cytoplasm and nucleus in a cell-type-specific manner (e.g., GR β actions are restricted to its dominant-negative effects on GR α -mediated responses) (31,32). Notably, GR β can bind to the glucocorticoid antagonist, RU-486 (mifepristone) (33), which has an inhibitory effect on GR β -coupled prostate cancer cell proliferation (34).

Similarly, GR and AR are both belong to the nuclear receptor superfamily, sharing the same chromatin binding domains (16,35). In some situations, the expression of GR may be upregulated during treatments of CRPC as well as parts of genes related in the AR-related signaling pathways. Pühr *et al.* (36) pointed out that GR expression is reduced in primary prostate cancer, restored in metastases, and correlates with reduced progression-free survival in relapse patients. Sahu *et al.* (37) found that the cistromes and transcription programs of GR and AR showed significant overlaps. Researchers exposed LNCaP-1F5 and VCaP cells to nonsteroidal antiandrogens and found half of the GR cistromes overlaps with the AR cistromes by ChIP-seq with the help of *FoxA1* protein. Arora *et al.* (23) pointed out that the expression of GR was increased when AR was potentially inhibited by enzalutamide, which re-expressed about 50% of AR-responsive genes and promoted tumor proliferation. In other ways, Wu *et al.* (38) designed GR/AR dual antagonist based on the similarity in sequence and structure of GR and AR binding sites (hormone binding pocket). They predicted 10 compounds and picked out compound Z19. This compound directly binds to AR and GR and inhibits the proliferation of prostate tumor cells *in vitro*. However, a phase I/II trial (39) designed to apply dual AR-GR antagonism (Enzalutamide and Mifepristone) in CRPC patients reported that the addition of mifepristone to enzalutamide following a 12-week enzalutamide lead-in did not delay time to PSA, radiographic or clinical PFS.

Genomic and non-genomic effects of GRs

The effects of GRs are mediated by classical genomic and alternative non-genomic mechanisms. In classical genomic methods, the interaction between GRs with either GREs on the DNA or the negative GRE mediates the regulation of gene expression (40). Rapid non-genomic effects mainly include: (I) specific interactions with membrane-bound

GRs; (II) non-specific interactions with plasma membranes; and (III) a specific interface with cytosolic GRs (41,42) which can affect mitochondrial function within seconds. However, an exploration of the non-genomic action of GRs in prostate cancer is still incomplete. An explanation for the development of androgen-dependent prostate cancer to hormone-independent prostate cancer is the point mutation of AR (43) and therefore the development of drug resistance. *SGK1* is a known target gene induced by ARs and GRs, and plays an important role in GR-mediated CRPC progression (22). The inhibition of androgen-induced genes shows that GRs can regulate the expression of AR-target genes without ARs, which suggests that GRs can bypass the AR inhibition of drugs by regulating different but overlapping transcriptomes to make the tumor appear hormone-independent (23). This also suggests that there is a mechanism for tumor drug resistance; that is, increasing the expression of GRs.

Glucocorticoids as therapeutic agents

Glucocorticoids belong to the steroid family, mainly synthesized in the adrenal glands, which are released in response to stress and in a circadian way (44,45). Glucocorticoids are widely used in the treatment of inflammatory and autoimmune diseases and organ transplantation. It is worth noting that the dosage and usage of glucocorticoids should be strictly controlled because of their short-term or long-term side effects (46-48), such as hyperglycemia (49-51), adrenal insufficiency (52), osteoporosis (53), and Cushingoid features (54).

Glucocorticoids have played an important role in the treatment of leukemia and several solid tumors, relieving the discomfort of chemotherapy drugs in the past decades. During the treatment of childhood leukemia, glucocorticoids were used as the first choice, which may regulate the expression of a series of apoptosis-related genes (55). The death-associated protein named *DAP* acts as a positive mediator of programmed cell death that is induced by interferon-gamma. Hulkko *et al.* (56,57) reports that *DAP3* interacted with GR mainly via the N-terminal region of *DAP3*, modulating the cytoplasmic GR-hsp90 complex, finally induced apoptosis. Wang *et al.* (58) found that mometasone furoate could inhibit proliferation and migration of acute leukemia cells via regulating PI3K signaling pathway.

In the treatment of prostate cancer, synthetic glucocorticoids are extensively used in practice as an

integral part of regimens based on their anti-inflammatory, the suppression of adrenal androgen synthesis and other benefits (59–61). However, evidences showed that the use of glucocorticoids may contribute to tumor progression in CRPC (15–17). In a post hoc analysis of the COU-AA-301 trial (62), corticosteroid use at baseline was associated with a worse overall prognosis, but not with less response to abiraterone. Woods-Burnham *et al.* (63) reported that glucocorticoids could induce therapy resistance-related stress oncoproteins. Stress oncoproteins Clusterin (CLU) and Lens Epithelium-Derived Growth Factor p75 (LEDGF/p75) were upregulated in response to standard PCa therapies (64–67). Knocked-down of GR by short inhibitory RNAs (siRNAs) reduced two proteins. Possibly there are multiple putative GR binding sites within the LEDGF/p75 and CLU promoters via *in-silico* analysis. Ortiz-Hernandez *et al.* (68) demonstrated that a group of interactome (*JPO2*, *MEN*, *MLL*, *IWS1*, *ASK1*, and *PogZ*, as well as transcription factors *c-MYC* and *HRP2*) may interact with integrase binding domain of LEDGF/p75, contributing to the survival, clonogenicity, and tumorsphere formation of docetaxel-resistant prostate cancer cells. However, the lack of researches and clinical trials still brings difficulties to define what extent glucocorticoids and GR contribute to the chemotherapy resistance.

Clinical trials in last 5 years

Prednisolone, dexamethasone, and prednisone are the major glucocorticoids applied in prostate cancer treatment. Under the guidelines (69), abiraterone combined with prednisone is a first line treatment for advanced prostate cancer. Due to adverse drug reactions, dexamethasone may be used in other combination therapies, such as those with ketoconazole. In the last 5 years, clinical trials or retrospective studies have focused on novel drugs based on the mechanism of selective inhibition or the applications of combination therapies. We chose studies from the ClinicalTrials database and EudraCT database and some retrospective studies from the NCBI database published in the last 5 years. The selected studies explored the effect of dexamethasone (70–76), prednisone (77–93), and prednisolone (94) (see *Table 2*).

The PSA response rate of dexamethasone is approximately 11.1–76.8%, and prednisone and prednisolone have been reported to have PSA response rates of 17.0–88.1% and 42.7%, respectively. Research has shown that the median time to PSA progression of prednisone is 5.0–18.6 months, while that of dexamethasone is 8.6–12.0 months (see *Table 2*) on CRPC.

Dexamethasone is usually administered with endocrine therapy drugs or other anti-tumor drugs, such as docetaxel, ketoconazole, imatinib, peptide cancer vaccine, and cyclophosphamide. A phase II, single-center trial (NCT01036594) sought to determine whether the administration of ketoconazole/dexamethasone, after disease progression, with ketoconazole/hydrocortisone slows or reverses disease progression. The results suggested that the number of participants who experience a $\geq 30\%$ decline in PSA after change from ketoconazole with hydrocortisone therapy to ketoconazole with dexamethasone therapy was 8 (25%). However, low patients' number included in this clinical trial left a question open. Another retrospective study evaluated the safety and activity of a steroidal switch from prednisone to dexamethasone in patients with advanced, heavily pre-treated CRPC (76), and found that 11% of the patients (4/36) showed a PSA decrease ($\geq 50\%$). Thus, switching medications could be an option for patients who have previously responded well to abiraterone acetate treatment. Interestingly, a randomized, open-label phase 2 study (93) designed for assessment of the safety of glucocorticoid regimens in combination with abiraterone acetate showed that patients ($n=42/164$) took 1,000 mg abiraterone acetate with 0.5 mg dexamethasone once daily orally (other three groups: 1,000 mg abiraterone acetate with 5 mg prednisone twice daily/5 mg prednisone once daily/2.5 mg prednisone twice daily) had highest PSA response rate (88.1%; 95% CI: 75.0–94.8%) and longest radiographic progression-free survival time [26.6 months (95% CI: 20.9–not evaluable)]. Although this trial provides results consistent with the approved use of abiraterone acetate with prednisone, 5 mg, twice daily for the treatment of metastatic castration-resistant prostate cancer (mCRPC).

Generally, in clinical studies, 1 mg of dexamethasone is administered orally every day. Recently, Mehra *et al.* (70) evaluated the effects of low-dose steroids on neutrophil-to-lymphocyte ratio (NLR) in patients suffering from CRPC, and found treatment-naïve CRPC patients with a high baseline or higher NLR values during treatment did not appear to benefit from low-dose corticosteroids. Zhu *et al.* (75) injected 10 mg of dexamethasone intravenously in 100 mL normal saline on the 1st day of the 3-week paclitaxel liposome protocol, and their PSA-based evaluation revealed that the therapy was effective in 14 cases (35%), and the median survival time was 17 months.

Over the last 5 years, prednisone was the most used steroid hormone in the endocrine therapy of CRPC. Recent studies have reported combinations with abiraterone acetate,

Table 2 Clinical studies of glucocorticoids in CRPC in the last 5 years

| Study | Dosage | N | PSA response rate (%) | PFS or OS* (month) | Median time to PSA progression (month) |
|----------------------------|---|-------|-----------------------|--------------------|--|
| Dexamethasone | | | | | |
| NCT00427999 | 1 mg QD | 65 | 37.7 | | |
| NCT01036594 | Hydrocortisone: 20 mg po QAM + 10 mg po QPM, dexamethasone: 0.5 mg po BID | 32 | 25.0 [#] | | |
| Mehra (70) | 0.5 mg po QD or prednisone 5 mg po BID | 75 | 31.6 | 25.6* | |
| Tanaka (71) | 0.5 mg po BID | 75 | 76.8 | | 12.0 |
| Calvani [§] (72) | 1 mg po QD or prednisone 10 mg po QD | 37 | 51.0 | 11.0 | |
| Nakai [§] (73) | 0.5 mg po BID or prednisone 5 mg po BID | 82 | | | 8.6 |
| Noguchi (74) | 1 mg po QD | 51 | 53.8–56.5 | 7.4–8.9 | |
| Zhu [§] (75) | 10 mg ivgtt ONCE | 41 | 35.0 | 17.0* | |
| Roviello [§] (76) | 0.5 mg po QD | 36 | 11.1 | 2.5 | |
| Prednisone | | | | | |
| NCT00642018 | 5 mg po BID | 149 | 56.1–56.9 | 8.6–9.0 | |
| NCT01940276 | 5 mg po BID | 100 | 66.0–74.0 | 16.6–16.8 | |
| NCT01666314 | 5 mg po BID | 137 | 17.0–50.0 | | |
| NCT02217566 | 5 mg po BID | 46 | 57.5 | 29.6* | 7.3 |
| NCT01695135 | 5 mg po BID | 214 | 54.5 | | 5.6 |
| NCT01193257 (77) | 5 mg po BID | 1,099 | 24.9 | 8.3 | 5.5 |
| NCT01084655 (78) | 5 mg po BID | 37 | 59.0 | | 6.8 |
| NCT02097303 (79) | 5 mg po BID | 36 | | | |
| NCT01308580 (80) | 5 mg po BID | 1,200 | 29.5–42.9 | 2.9–3.5 | 5.7–6.8 |
| NCT01637402 (81) | 5 mg po BID | 41 | | | 12.0 |
| NCT01511536 (82) | 5 mg po BID | 37 | 46.2 | | 6.9 |
| NCT01393730 (83) | 5 mg po QD | 40 | 60.0 | | 5 |
| NCT01193244 (85) | 5 mg po BID | 1,560 | 24.6–42.6 | 13.8 | 5.59–8.3 |
| NCT01308567 (86) | 5 mg po BID | 1,168 | 60.7–68.7 | 4.4–5.3 | 8.2–9.2 |
| NCT01543776 (87) | 5 mg po BID | 72 | 50.0–58.0 | 8.6 | |
| NCT01204710 (89) | 5 mg po BID or 5 mg po QD | 121 | 22.6 | 2.3 | |
| NCT00887198 (90) | 5 mg po BID | 1,088 | | 30.0–34.0* | 11.1 |
| NCT01718353 (91) | 5 mg po BID | 63 | 55.6 | 9.1 | |
| van Dodewaard-de Jong (84) | 5 mg po BID | 88 | 56.5–61.9 | 9.8 | |

Table 2 (continued)

Table 2 (continued)

| Study | Dosage | N | PSA response rate (%) | PFS or OS* (month) | Median time to PSA progression (month) |
|------------------|---|------|-----------------------|------------------------|--|
| Yu (88) | 5 mg po BID | 74 | 24.0–47.0 | | 13.9–17.9 |
| Posadas (92) | 5 mg po BID | 57 | 32.0 | | |
| Attard (93) | 5 mg po BID or 5 mg po QD or 2.5 mg BID or dexamethasone 0.5mg QD | 164 | 60.0–88.1 | 12.8–26.6 [§] | 4.83–18.56 |
| Prednisolone | | | | | |
| NCT01685983 | 5 mg po BID | 82 | 42.7 | | 4.7 |
| NCT00268476 (94) | 5 mg po QD | 1974 | | | Not reached |

[§], research studies marked “[§]” in the “Study” column indicates a retrospective study; #, values marked “#” in the “PSA response rate” column indicates a decline of PSA $\geq 30\%$; *, values marked “*” in the “PFS or OS” column indicates it is the value of OS. [§], values marked “[§]” in the “PFS or OS” column indicates it is radiographic PFS. Some data in this study (NCT00268476) had not reached median time. PSA response rate: A decline of PSA $\geq 50\%$. CRPC, castration-resistant prostate cancer; PSA, prostate-specific antigen; PFS, progression free survival; OS, overall survival; po, oral; QD, quaque die; QAM, every morning; QPM, every evening; BID, twice daily; ivgtt, intravenous drip; ONCE, only once.

docetaxel, cabazitaxel, Ra-223, orteronel, dutasteride, and apalutamide (77–84,92,93,95,96). Yu *et al.* (88) evaluated the effectiveness of intravenous apatersen with oral prednisone (5 mg, twice daily) or prednisone alone, and observed a PSA decrease $\geq 50\%$ in 47% of patients in the apatersen with prednisone group compared to a decrease of 24% in the prednisone only group. In these reports, the use of steroid hormones was adjusted according to patients' adverse reactions. However, few studies have compared dexamethasone or prednisone with a placebo. Thus, it is difficult to compare the efficacy of different steroid hormones.

Conclusions

Various GR isoforms may play an important part in the development of CRPC; however, the mechanism of CRPC remains complex and unclear. Most clinical trials in the last 5 years have focused on the use of prednisone. Only 1 clinical trial included a comparison of dexamethasone and hydrocortisone in its sequential treatment design. In short, GRs, including their isoforms, are involved in the progression of prostate cancer and may have implications on advanced treatment options. Further research is necessary to assess and attempt to understand and create hypotheses with GRs and the progression of prostate cancer more fully.

Acknowledgments

The authors appreciate the academic support from AME Prostate Cancer Collaborative Group.

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at <https://tau.amegroups.com/article/view/10.21037/tau-22-501/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tau.amegroups.com/article/view/10.21037/tau-22-501/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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- (English Language Editor: L. Huleatt)

Cite this article as: Zhou F, Shi Y, Zhao G, Aufderklamm S, Murray KS, Jin B. A narrative review of the role of glucocorticoid receptors in prostate cancer: developments in last 5 years. *Transl Androl Urol* 2022;11(8):1189-1199. doi: 10.21037/tau-22-501

Table S1 Detailed search strategy of NCBI database

| Items | Specification |
|---|--|
| Date of search (specified to date, month, and year) | 2022.06.01 |
| Databases and other sources searched | NCBI database |
| Timeframe | 2015.03–2022.01 |
| Search terms used | “glucocorticoids” [Mesh] AND “prostate cancer” |
| Result | Finally got 34 studies. Then traverse and filter the literature one by one |
| Search terms used | “Prednisone” AND “CRPC” |
| Result | Finally got 49 studies. Exclude literature read before then traverse and filter the literature one by one |
| Search terms used | “Prednisolone” AND “CRPC” |
| Result | Finally got 13 studies. Exclude literature read before then traverse and filter the literature one by one |
| Search terms used | “Dexamethasone” AND “CRPC” |
| Result | Finally got 11 studies. Exclude literature read before then traverse and filter the literature one by one |
| Search terms used | “Prednisone” AND “castration-resistant prostate cancer” |
| Result | Finally got 223 studies. Exclude literature read before then traverse and filter the literature one by one |
| Search terms used | “Prednisolone” AND “castration-resistant prostate cancer” |
| Result | Finally got 60 studies. Exclude literature read before then traverse and filter the literature one by one |
| Search terms used | “Dexamethasone” AND “castration-resistant prostate cancer” |
| Result | Finally got 30 studies. Exclude literature read before then traverse and filter the literature one by one |

NCBI, the National Center for Biotechnology Information database; CRPC, castration-resistant prostate cancer.