Adverse events due to glucocorticoids in ANCA-associated vasculitis are frequent but reporting should improve

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INTRODUCTION

High dose glucocorticoids (GCs) are an integral part of induction therapy in ANCA-associated vasculitis (AAV).

There are concerns from clinical studies over the adverse impact of GCs in AAV both in terms of acute and chronic clinical problems. High dose GCs may be associated with the risk of infection and thus early mortality in AAV. With longer treatment and/or repeated courses of GCs there is a risk of cumulative organ damage and increased cardiovascular risk.

The adverse event profile of GCs is well known and is associated with unmet medical need to reduce GC exposure in diseases such as AAV as long as the underlying disease can be managed effectively with other therapies.

This study aimed to examine the scope of GC adverse events (AE) in AAV by performing a systemic literature review to examine AEs directly attributed to GCs in clinical studies in AAV patients.

METHODS

STUDY DESIGN. Systematic literature review (Medline and EMBASE) – studies relating to AAV only reported in this communication.

STRATEGY. Search was performed for studies in humans published from 1 Jan 2007 up to 30 Jan 2018.

INCLUSION & EXCLUSION CRITERIA. Studies were excluded if they were case reports or if they reported only GC efficacy. This literature review aimed to quantify risk of GC related AEs relating to precise GC dose and duration and initial searching demonstrated a relative paucity of studies which reported this information in AAV patients. Therefore the systematic review inclusion criteria were widened to include diseases with analogous relapsing remitting course and a similar GC regime. Therefore inclusion criteria were studies reporting adverse events related to GCs in AAV, pemphigus, systemic lupus erythematosus, giant cell arteritis and glomerulonephritis. Data relating to the AAV studies only are presented here.

DATA ANALYSIS. Studies were reviewed and data on GC-related AEs (any untoward medical occurrence) and serious AEs (SAE, defined in European Medicines Agency CPMP/ICH/377/95) which threatened life or function were extracted.

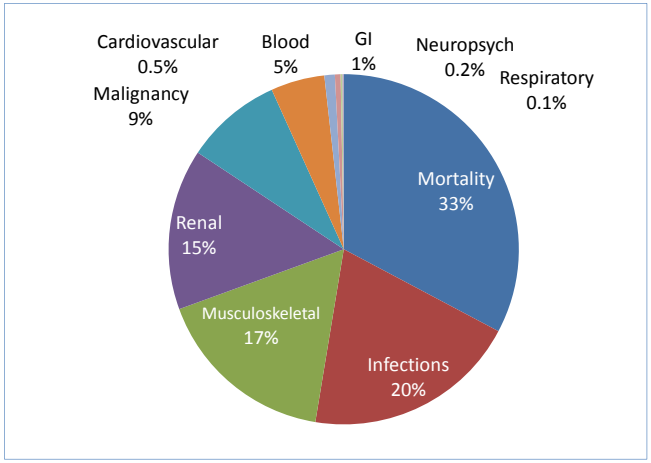
Description	Total number of articles
Literature search (1st Jan 2007 to 30th Jan 2018)	3462
Filters	• Human • Year 2007 to 2018 • English article
Exclusion criteria	• Case reports • Publication mentioning only efficacy of glucocorticoids
Inclusion criteria	Adverse events related to glucocorticoids in indications • Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis (AAV) • Pemphigus • Systemic Lupus Erythematosus • Giant Cell Arteritis • Glomerulonephritis
De-duplication	3232
Relevant articles	317
Articles included for Analysis	267
Articles where data not available	50
AAV articles included for analysis	33
Selected articles included for analysis	38

RESULTS

Table 1 GC adverse event reporting in 33 AAV studies. GC related adverse event reporting is often incomplete with not all studies reporting either SAEs or AEs or both categories. Nevertheless in clinical studies which do report adverse events, GC related AEs are common.

	Serious adverse events	Adverse events
Number of studies reporting events	23	17
Number of patients exposed to glucocorticoids in these studies	3543	22278
Number of patients reporting GC adverse events in these studies	1102	4284
Percentage of patients experiencing adverse events	31%	19%

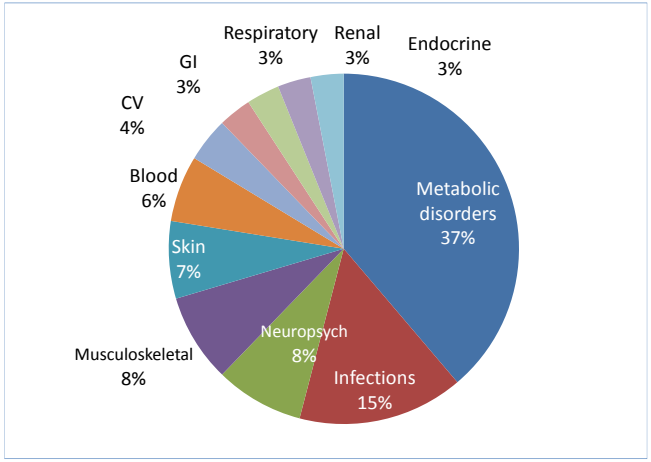
Figure 1 GC related serious adverse events Mortality is presented here as the most common SAE but infections , musculoskeletal and renal disorders are frequent.



Serious adverse event	Detailed insight
Mortality	Infection was the leading cause of death linked to a GC SAE and was particularly noted early in induction treatment
Infections	Clinical details were rarely given simply being described as serious/severe infections in 73% of these reports and pneumonia in 9%. In EUVAS studies up to 50% infection occurred within 2 months of treatment commencing
Musculoskeletal	96% bone fracture and 4% osteonecrosis
Renal disorders	Reports were related to nephropathy, kidney failure and nephritis – related to AAV
Malignancy	Most commonly reported were bowel, skin, prostate and haematological cancers

RESULTS

Figure 2 GC related adverse events Metabolic disorders are common but infections, musculoskeletal and skin disorders are also common



Adverse event	Detailed insight
Metabolic	83% of reports related to diabetes whereas 8% were hyperphagia and 8% weight gain
Infections	Causes were rarely given with 79% of AE reports being "general infection" with 17% viral and 3% bacterial
Neuropsychological	61% were related to psychiatric disorders including irritability, anxiety, depression and hyperactivity
Musculoskeletal	65% were muscular disorders, in particular muscular weakness, and osteoporosis in 34%
Skin	Reports included pigment disorders (58%), hirsutism (36%), acne (5%) and cutaneous eruptions (1%)

CONCLUSIONS

Reporting of GC related adverse events in AAV can be improved and overall there appears to be under reporting or the events are not attributed to GCs within the study. The adverse event profile of GCs is well known and this may contribute to the reporting frequency.

However, serious adverse events and adverse events are common in the studies which report them. There is significant mortality and infections, particularly early in the course of AAV treatment are commonly reported. Details of infection related serious adverse or adverse events eg site, severity, cause are rarely given in AAV studies

Musculoskeletal disorders are a clinical challenge with fractures being a common serious adverse event and muscular weakness a common adverse event.

Metabolic disorders, in particular, diabetes mellitus are common and add to the overall patient burden.

GC related adverse events are an unmet medical need in AAV and new therapeutic options should aim to improve the overall profile of treatment related adverse events as well as controlling vasculitis activity

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