# Adverse Events due to high dose glucocorticoids – Lessons from ANCA-associated vasculitis and other inflammatory diseases

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## BACKGROUND

**Glucocorticoids (GCs) are a cornerstone in the treatment of rheumatic diseases and are also administered, often in higher doses (>7.5mg), in many other rheumatic diseases such as lupus or vasculitis [1]. Although high-dose GCs are a mainstay of induction remission therapy in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), they have never been systematically studied in randomized controlled trials [2]. Nevertheless, the side effect profile of GCs is well established and the cumulative exposure to GCs is known to contribute to the morbidity and mortality associated with AAV, i.a. related to organ damage, infections and cardiovascular diseases [2, 3]. However, studies on GCs in general lack a systematic assessment of adverse events (AEs) and defining and reporting AEs during GC-therapy is often incomplete in literature data [1, 4]. The EULAR Task Force on GCs pointed out that even after 60 years of GC in clinical practice, there are no reliable data on the incidence of AEs and made specific recommendations for reporting GC-related AEs in clinical trials [4].**

## OBJECTIVES

This systematic literature review was carried out to examine AE rates and outcomes related to high dose GC use in AAV and to quantify AE risk in terms of GC dose and duration of GC therapy.

## METHODS

- A systematic literature review of studies published between 1 Jan 2007 and 30 January 2018 was performed.
- Data on GC-related AEs (defined as any untoward medical occurrence) and serious AEs, i.e. AEs in their most severe form threatening life or organ function (defined in European Medicines Agency CPMP/ICH/377/95) [5] , were extracted from identified trials.
- Against the background of the general EULAR recommendations on monitoring of AEs, the initial AAV search yielded incomplete GC data collection for most AAV studies. Therefore, the search strategy was extended to include other inflammatory diseases using similar GC regimes at comparable doses, namely systemic lupus erythematosus, glomerulonephritis, pemphigus and giant cell arteritis.
- The consensus-based EULAR recommendations on monitoring of GC-related AEs in clinical trials include the following three general recommendations [4]:
  - Report all monitoring results of trials
  - Report both on the group level (eg, means) and on the individual patient level (eg, numbers)
  - Develop new tools for assessing specific AEs

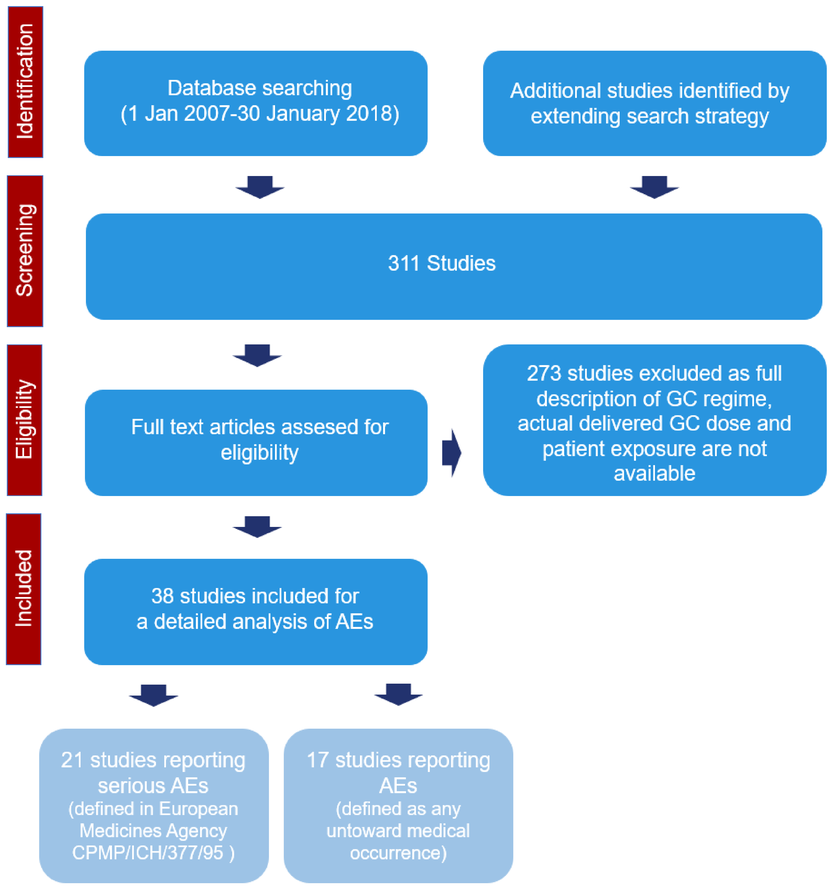
## RESULTS

- Based on the extended search strategy including four other terms, three hundred and eleven studies were identified in which GC-related AEs were published (Figure 1).
- Thirty-eight studies were selected for a detailed AE analysis on the basis of their inclusion of full description of GC regime, actual delivered GC dose and patient exposure.
- Of the 62,630 patients enrolled in the thirty-eight studies, 35,587 were exposed to GCs (Figure 2).
- Twenty-one studies reported serious AEs, while seventeen studies reported AEs only.

## RESULTS (cont.)

- The most common serious AEs were related to specific organ damage – particularly musculoskeletal, ocular and neuropsychiatric – but mortality and infection were also observed (Table 1).
- The most common AEs were metabolic conditions, with diabetes mellitus related events comprising 72%, and weight gain comprising 15% of the metabolic AEs.
- Correlation analysis demonstrated that mean total GC dose was positively related to the risk of death (r = 0.51) and infection (r = 0.49) while duration of GC therapy was related to risk of infection (r = 0.62).

**Figure 1 – Flow Chart of selection and inclusion of studies** Systematic literature review of studies using the MEDLINE (PubMed) database – advanced search criteria included AAV, systemic lupus erythematosus, glomerulonephritis, pemphigus and giant cell arteritis




## RESULTS (cont.)

**Figure 2 – Number of patients GC-exposed and reporting GC-related events** In 38 studies included in the systematic literature review, 35,587 patients were GC-exposed.

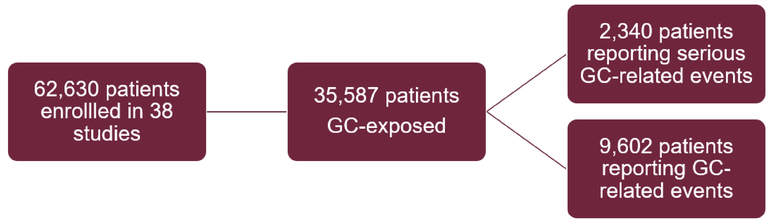



**Table 1 – Reported GC-related events** Most common serious AEs /AEs (%) were related to specific organ damage, mortality or infection.

| Reported Adverse Events (AEs) | Serious AEs | AEs |
|---|---|---|
| Events reported n / (%) | 840 / 2340 (36%) | 2479 / 9602 (26%) |
| Most common events (%) | Organ damage (49%)<br>Death (14%)<br>Infection (7%) | Metabolic* (50%)<br>Musculoskeletal (16%)<br>Ocular (14%)<br>Infection (12%) |

*Diabetes mellitus (72%), weight gain (15%)

## CONCLUSIONS

**GC-related AE reporting in clinical studies of high dose GCs could be improved. Serious AEs including organ damage, infection and mortality were reported and both factors, total GC dose and duration of therapy are important risk factors for mortality and infection. Metabolic and musculoskeletal events represent a particular patient burden. New therapeutic options for AAV and other rheumatic diseases should aim to improve this medication-related AE profile.**

## REFERENCES

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