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Glucocorticoid therapy in ANCA Vasculitis – using the Glucocorticoid Toxicity Index as an outcome measure

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Key Points

- Glucocorticoid Toxicity Index provides a global quantifiable assessment tool to assess glucocorticoid associated morbidity.
- Cumulative doses of steroids in ANCA associated vasculitis leads to worse glucocorticoid related toxicity
- Whilst glucocorticoids remain the mainstay of AAV treatment, the narrow therapeutic window supports the need for GC-sparing treatments

Abstract

Background

Anti-neutrophil cytoplasm antibodies (ANCA) associated vasculitis (AAV) is an autoimmune disease. Induction remission and maintenance treatment typically includes high dose, tapering glucocorticoids (GC) in addition to other immunosuppressive medication. The use of Glucocorticoid Toxicity Index (GTI), provides a global, quantifiable assessment tool in which clinicians can assess GC associated morbidity. Recent trials in AAV have exposed the need for systemic assessment of GC burden. In this small cohort study, we look to address these issues and the justification of newer GC sparing agents such as C5a inhibitors.

Methods

A retrospective cohort study of 43 patients with biopsy AAV was constructed from a single centre between 2012 to 2016 and followed up for 48 months. The GTI table made up of adverse features used to quantify patients GC toxicity. Electronic patient records were reviewed and scores calculated according to published methods. GTI scores were compared with cumulative steroid doses at separate intervals as well as incidences of adverse features in relation to the treatment timeline.

Results

The mean age was 65.9 (± 11.06) years and treatment regimens consisted of glucocorticoids alongside cyclophosphamide or rituximab. Our results showed statistical significance in the association of cumulative GC doses and GTI scores (p=0.008, 95% CI, 1.31 to 8.05). Adverse features relating to mood disturbance and GC induced psychosis occurred early, in contrast to adrenal insufficiency which typically presented later in the follow up. Infection related adverse events were consistent throughout.

Conclusions

We demonstrated that higher, cumulative doses of steroids in AAV lead to worse glucocorticoid related toxicity. Using the GTI creates potential to individualise and quantify the adverse effects patients experience as a result of GC treatment and permits more patient centred management. Whilst glucocorticoids remain the main adjunctive immunosuppression of AAV treatment, the narrow therapeutic window supports the need for GC-sparing treatments.

Introduction:

Anti-neutrophil cytoplasm antibodies (ANCA) associated vasculitis (AAV) is a complex autoimmune inflammatory disorder. It is characterised by inflammation and necrosis of small and medium sized blood vessels leading to tissue destruction and organ dysfunction. Immunosuppression is the mainstay of treatment.

The European Vasculitis Society (EUVAS) has conducted several large randomised control trails addressing various aspects of AAV treatment (1). The role of the role of B-cell depletion, cytotoxic and antimetabolite therapy in remission induction and remission maintenance therapy is well supported (1,2).Induction and maintenance treatment typically involves adjuvant glucocorticoid (GC) treatment and as a result, many AAV patients receive long term, high cumulative doses of GC as management of their AVV and any relapsed disease.

With the exception of the recent PEXIVAS (3)and ADVOCATE (4) trials, there is a lack of evidence substantiating the role of glucocorticoid dosing and duration, with significant evidence of treatment related harm (5). The detrimental consequence of increasing GC doses has long been cited and the effects were recognised back in the 1950's when steroids were given for many systemic diseases (6–8). Many of the side effects seen in autoimmune conditions such as AAV are often related to the duration of GC therapy (5,9). Adverse features can include steroid induced diabetes, hypertension, osteoporosis, cataracts and adrenal insufficiency (6,7,9).

In more recent years there has been a gradual trend towards minimising exposure to high dose corticosteroids including pulsed methylprednisolone especially in high risk or frail patients(10,11). This is also seen in other areas of nephrology, for example where GC treatment was once the mainstay treatment in the prevention of rejection in solid organ transplant medicine. However, steroid free transplantation is becoming increasingly common in order to reduce GC related toxicity(12,13). These practise-based changes and recent studies have in part shaped the way we approach GC prescribing but it still remains a relatively evidence free area especially with regards to the use of methylprednisolone.

More recently, the term glucotoxicity has been coined and this has brought about the introduction of the Glucotoxicity index (GTI) (6). The GTI is a global assessment tool which clinicians can use to quantitively assess the toxic effects of GC therapy and its associated morbidity at time intervals (6). Whilst the adverse effects of GC are well known there is a lack of substantial data quantifying adverse outcomes or incidence of steroid related side effects (14). In 2014 Robson et al (5) demonstrated significant adverse effects relating to the duration of GC use in AAV. GC treatment contributed to the vasculitis damage index and this was of particular significance given those with a high index had an associated increased mortality (5,15). They demonstrated worsening outcomes over long term follow up and recommended clinicians to reduce GC use(5).

The measurement of glucocorticoid related toxicity varies significantly in published data (6,14)and is often confounded by the impact of other concurrently administered immunosuppression. This study aims to evaluate the GTI in AAV as a as a comprehensive

and quantitative tool of assessing the steroid associated treatment burden in current management strategies. Recent trials in AAV have exposed the need for systemic assessment of GC burden. In this small cohort study, we look to address these issues and the justification of newer GC sparing agents such as C5a inhibitors.

Materials and Methods

Data collection

A cohort study of 43 ANCA positive patients with biopsy proven pauci-immune glomerulonephritis was constructed from a single centre between 2012 and 2016. Each patient was followed up for a total of 48 months. Patients who did not have a biopsy or where the biopsy was non diagnostic or demonstrated significant dense deposit disease were excluded. In addition, those with positive anti- glomerular basement membrane antibodies, dual pathology and secondary vasculitis were also excluded. Data was collected retrospectively and GTI scores were collated from electronic patient records and telephone calls with some patients. Cumulative doses of GC were calculated alongside GTI scores at seven separate intervals; 1, 3, 6, 12, 24, 36 and 48 months. Pulsed methylprednisolone at induction and relapse were reviewed and doses were converted to oral prednisolone dose equivalents, with all subsequent cumulative doses presented as prednisolone (mg).

The primary outcome measures include the GTI scores alongside the cumulative steroid doses. Secondary outcome measures include the incidences of each adverse event and the timeline in which each event occurred in relation to commencing GC therapy.

GTI scoring system

The GTI is a tool which clinicians can use to validate and quantify the toxic effects of GC therapy at time intervals. Patient information from our cohort was compared against the glucocorticoid toxicity index in which there is a composite and specific list (Table 1). Each patient was given a score relating to features on the composite list and this exercise was repeated at 7 separate intervals. This allowed for the measurement of change in the GTI over the 48 months follow up period.

The items listed relate to commonly recognised adverse events as a result of cumulative steroid exposure. Scores range from - 36 to 439 with Cumulative Worsening Score (CWS) relating to an increase in GC toxicity burden. The Aggregate Improvement Score (AIS) is a negative score, reflecting an improvement in toxicity (16). The full details of the GTI scoring system, categories and components are described in the paper by Miloslavsky et al (6).

Statistical Analysis

Differences of quantitative parameters between groups were assessed using both t and rank sum tests. 95% confidence intervals (CIs) are reported and the threshold for statistical significance throughout was a P value of less than 0.05. Repeated measures of GTI and steroid doses were summarised by the area under the curve and modelled using linear regression with backward selection. All statistical analyses were conducted in STATA V.16. For continuous variables, means and standard deviations were calculated and median and interquartile range for continuous variables with skewed distribution.

Ethical Approval

Approval for this study was obtained by The Centre for Health Research and Innovation on behalf of Lancashire Teaching Hospitals NHS Foundation Trust (Ref: SE-317). The study was approved as service evaluation, therefore formal ethics committee review was not required.

Results

Study Population

Forty-three patients were identified, 23 female and 20 males with a mean age of 65.9 (± 11.06) years at the time of presentation. All patients were ANCA positive: 44.2% (n= 19) positive for proteinase 3 (PR3) ANCA antibodies and 55.8% (n= 24) positive for myeloperoxidase (MPO) auto-antibodies and had a renal biopsy at diagnosis demonstrating evidence of pauci-immune glomerulonephritis. Baseline patient characteristics with subgrouping according to ANCA serology is outlined in Table 2 with no meaningful difference in age or gender across the two groups. One patient was lost to follow up, five patients died and one patient received a renal transplant during the follow up period.

All patients had AAV with renal involvement and 69.8% had more than one system involvement, with three patients having more than five systems involved. The mean estimated glomerular filtration rate (eGFR (ml/min/1.73m^2)), at presentation was 23.3ml/min (± 18.1ml/min) with eight patients requiring initial renal replacement therapy. Of these eight patients, six (75%) regained independent renal function later in the study. Eight patients experienced relapsing disease during the follow up period and 2 patients reported worsening ENT disease on weaning GC's.

Treatment

Induction therapy consisted of either intravenous cyclophosphamide or rituximab alongside daily oral GC. Pulsed intravenous methylprednisolone and plasma exchange were administered according to physician discretion. The dosing regimen of cyclophosphamide was adjusted for age and renal function in line with recommendations made by the European Vasculitis Study Group (2). The median cumulative dose of cyclophosphamide given was 5.4g (IQR 2.4-2.9g). Rituximab was administered at a dose of 1g every two weeks for two doses. The dose taper of oral GC followed the regimen outlined by the CYCLOPS trial with variation according to physician discretion. Within the overall patient cohort, two patients died during the induction period, one as result of vasculitis and the other from a cerebral vascular event.

Initial doses of oral prednisolone ranged between 60mg to 20mg daily. Intravenous pulsed methylprednisolone was given to 37.2% (n=16) of which most (n=12) received a total dose of 1.5 gram over 3 days. Two-thirds (65.9%) of patients had a 50% reduction in oral GC dose by week four. Of those receiving intravenous pulsed methylprednisolone the mean eGFR was 21.6 ml/min/1.73m^2 (8 - 22.3ml/min) at presentation and the majority (62.5%) had more than one system involvement.

Twelve patients received adjuvant plasma exchange with an average of 5.3 sessions. Within this subgroup, ten received concomitant pulsed intravenous methylprednisolone as part of remission induction therapy. The cumulative dose of prednisolone at 12 months was higher amongst patients receiving plasma exchange therapy; 5203.6mg vs. 4667.3mg. Remission maintenance therapy in the surviving 41 patients consisted of rituximab (n=17),

azathioprine (n=26), mycophenolic acid (n=3), methotrexate (n=3) and cyclophosphamide (n=1). 95.1% of those on maintenance therapy received concurrent daily maintenance oral GC.

Cumulative steroid doses were calculated at seven separate time intervals. At the end of the 48 months follow up period, over half (54.1%) of patients were steroid free. Of those who completed steroid therapy, the median GC treatment period was 34.5 months (IQR 24.2 – 41.8 months). Amongst the seventeen patients still receiving GC treatment at the end of the study period, one patient was receiving 10mg/day prednisolone as a part of a reducing course following recent relapse and the remaining nine patients were on 5mg/day or less of prednisolone daily.

GTI scores

GTI scores and cumulative steroid doses were calculated at fixed intervals. Scores ranged from 0 to 123 over the 4 year follow up period. Of the 37 patients included at the end of the study, only 12 patients (27.9%) had a GTI score of 0. Figure 1 shows the cumulative GC dose and GTI scores of individual patients at the end of the study period. With the exception of one patient, this demonstrates that at 48 months patients with a GTI score of over 60 had received over 9000mg of glucocorticoids. Using linear regression with backward selection, there was a statistically significant association demonstrated between the cumulative GC dose and GTI score with a p value of 0.008 and 95% confidence interval for the regression coefficient was 1.31- 8.05. There was no association between the use of pulsed intravenous methylprednisolone and GTI score at the end of the study period (p=0.8). Similarly, there was no difference in cumulative GC dose and GTI scores in those that were treated with cyclophosphamide (p=0.72) or rituximab (p =0.36).

Overall PR3 positive patients received higher cumulative doses of glucocorticoids than MPO positive patients at the end of the study period; 9330.5mg vs. 5665mg. In line with this a larger proportion of patients in the PR3 group had evidence of GC toxicity at follow up compared to those with MPO positivity, 73.7 vs. 65% respectively. There was no significant difference in relapse rates but higher mortality was associated with MPO positive disease (table 2).

Incidence of toxicity

The incidence of adverse features related to steroid therapy both from the composite and specific list increased over the follow up period. Three patients (7.0%) demonstrated GC toxicity as early as 4 weeks. At the end of the follow up period, 27 patients (71.9%) demonstrated GC toxic effects (Table 2).

Infections, reduced bone density and increasing BMI were the commonest adverse effects of GC therapy. Nearly a quarter (23.2%) had an improvement in their GTI score (AIS) during the follow up period, with the majority seeing an improvement in weight, glucose tolerance and blood pressure. The AIS occurred after the first year of treatment and following a reduction in the daily dose of GC.

Figure 2 outlines the distribution of adverse events related to glucocorticoid toxicity along the follow up period. As expected, certain dose dependant adverse features such as mood disturbance and steroid induced psychosis occurred early on in the treatment course. This is in contrast to adrenal insufficiency that occurred later in the follow up period, with a median time of 21 days (IQR 18-24) and 1059 days (IQR 895-1224) respectively.

Figure 3 shows the percentage distribution of specific GC related adverse effects. Weight gain, increased body mass index (BMI), steroid induced diabetes and gastrointestinal issues such peptic ulcer disease occurred mostly within the first year of treatment while reduced bone density and osteoporotic fractures occurred on average between two to three years into GC therapy.

Infection related adverse events were largely consistent throughout the duration of follow up as demonstrated in Figure 2. This can be attributed to baseline immunosuppression rather than GC alone. Five patients scored 19 on the composite list (table 1) for having oral candidiasis and or uncomplicated varicella zoster infections. Oral fluconazole treatment was prescribed to 90.2% (n=37) of patients and all patients that developed oral candidiasis received appropriate fluconazole prophylaxis. Six patients scored 93 points due to grade 3 infection which was defined as needing hospitalisation and or intravenous antibiotics. These infections occurred within the first year of commencing treatment. Co-Trimoxazole prophylaxis was prescribed in 97.6%(n=40) of patients and there were no incidences of Pneumocystis jirovecii infection.

Reduced bone density and fragility fractures were recognised in 24.4% and 7.3% of patients respectively. All three patients that suffered fragility fractures had evidence of reduced bone mineral density on Dual Energy X-ray Absorptiometry (DEXA) scan. Bone protection was prescribed in the form of bisphosphates, vitamin D replacement and calcium supplements. 80.5% (n=33) received calcium supplements and 36.5% (n=15) were treated with Bisphosphonates. Of those that didn't receive bisphosphonate treatment the median eGFR was 26 ml/min/1.73m^2 (IQR 13.5-46ml/min) which may have been a contributory factor.

Discussion

This retrospective study looks at the impact of prolonged exposure to glucocorticoids using a novel scoring system. Whilst the effects of GC toxicity are well recognised, there has not previously been a tool that enables clinicians to quantify the toxic effects of GC treatment at an individual level. There have been several studies demonstrating the correlation between steroid exposure and GC toxicity however with the exception of the recent ADVOCATE (4)trial, there have been no other studies that have evaluated GTI scores in the context of AAV. Our data demonstrated that higher cumulative doses of GC's led to more adverse effects of therapy and a quantitative increase in GC toxicity using this tool.

The concept of systematically measuring GC toxicity in the form of GTI is new and warrants further validation. A study in 2020 by McDowell et al (17) looked at a variation of the glucocorticoid toxicity index (GTI 2.0) in severe asthma. It demonstrated that GTI scores were not only associated with GC doses but also correlated with patient reported outcome measures (PROMS). Using tools such as the Mini-asthma quality of life questionnaire

(AQLQ), they demonstrated strong correlation with GTI scores and patients reported quality of life (17).

At present steroids remain a cornerstone of AAV treatment, but more recently studies are looking at ways in which to reduce steroid exposure. McGovern et al (10) looked at lower dose GC in the management of ANCA associated vasculitis in elderly and frailty groups. The median cumulative dose of prednisolone at 3 months in this study was slightly lower than the cumulative doses seen in our cohort; 2030 mg (IQR 1785–2167), 2520mg (IQR 1995-3495) respectively. The outcomes reported by McGovern et al (10) supported a low-dose glucocorticoid regime in favour of higher daily doses or pulsed methylprednisolone at induction. This was further supported by retrospective, multi-centre study of 114 patients in which pulsed IV methylprednisolone was associated with increased risk of infection and steroid induced diabetes and offered no benefit in the treatment of AAV compared to high dose oral corticosteroids (18).

In our present study, infection was the most common toxicity amongst our cohort with the incidence of infection occurring throughout the follow up period. Many patients experienced oral candidiasis and varicella zoster infections and some suffered more serious effects such as sepsis requiring hospitalisation. It is important to note that all patients in our cohort received steroids concurrent to other immunosuppressive therapies and therefore the specific role of GC in infection related toxicity is not in isolation. Furthermore, other vasculitic contributing factors such as damaged sino-respiratory mucosa may have also had a role in the development of infections.

Steroid induced mineral bone density disease was also noted in our cohort. Its incidence trended towards a delayed onset, correlating with a higher cumulative GC dose. One potential confounder is the demographic risk factors of our cohort (age > 60yrs and female gender). Similar features have been recognised in other publications (1) and the role of prophylactic bone protection is vital. Whilst over half the patients in our cohort were steroid free at 48 months, many continued on low dose, maintenance steroids further exposing them to collective side effects.

With larger trials such as PEXIVAS identifying non inferiority of lower dose GC treatment and potential reductions in the incidence of severe infection (3,11), it has made way for other trials to look at GC sparing treatments. Avacopan (CCX168) is a selective C5a receptor inhibitor which has been used as an adjuvant to reduce GC exposure significantly in the management of AAV. The recent landmark trial ADVOCATE(4) published earlier this year, has demonstrated that not only is avacopan effective in the management of AAV but reports significantly fewer adverse effects related to GC treatment compared to standard steroid treatment. It suggests that avacopan precludes the need for high dose glucocorticoid treatment in these patients (4,19,20). Furthermore, the trial used GC toxicity index as a secondary end point and demonstrated GTI cumulative worsening scores (GTI-CWS) that were higher in prednisolone group compared to the avacopan group(4). Not only does this promote the use of GC sparing agents and highlight the adverse effects of GC treatment supported by the findings in our cohort, but it also highlights the use of GTI in clinic trials and future research.

Within the world of nephrology, the use of steroids is not only limited to ANCA associated vasculitis. It is used as standard of care in the management of other conditions such as minimal change disease, membranous and IgA nephropathy. Whilst GC remain imperative to the treatment in many of these conditions, the narrow therapeutic index means that close observation and monitoring is essential.

The findings of our study should be considered within the context of its limitations. Firstly, we recognise that the observational nature of the study in addition to other confounds such as immunosuppressive medication, plasma exchange and active vasculitis are all potentially contributory to the development of adverse effects. It is not possible to fully attribute all the adverse effects discussed to glucocorticoid treatment alone. However, panel of scientific experts who developed the GTI defined the features to be included in the composite GTI list based on different domains (6). These included the likelihood of adverse features occurring in over 5% in patients exposed to GCs, with toxicity being more likely a result of the GC therapy than the disease itself. Additionally any measurements and scores were not dependent on or requiring invasive procedures or imaging (6). Other adverse features that were considered significant but had the potential be confounded by other features such as underlying disease or other treatments were included in the specific list. Secondly, the retrospective nature of our study may also lend itself to inaccuracies in the reporting and documentation of some mild side effects such as mood disturbance or skin changes. This is likely to have led to an under representation of the adverse features. Thirdly, our relatively small sample size may restrict the accuracy of our results.

Progressing the role of GTI in the assessment and management of renal patients treated with GC will be of significant value. Calculating a baseline GTI score at induction with prospective monitoring, will help identify those patients at increased risk of developing toxic effects from prolonged steroid exposure. It is well known that there is a degree of genetic predisposition to GC toxicity (21). The role of pharmacogenetics alongside tools such as the GTI will allow for more patient centred management and tailored treatment plans (22).

In spite of a relatively small cohort, this study has demonstrated the use of measuring GTI in AAV patients. We have shown that cumulative doses of steroids in AAV leads to worsening glucocorticoid related toxicity. Using the GTI tool allows us to individualise and quantify these adverse effects patients experience which in turn will improve patient centred management. We have also shown that the incidence of adverse features relating to GC exposure occur at different stages with a persistent risk of infection. This data supports the need for further work evaluating GC-sparing treatments, the assessment of steroid toxicity and its relation to clinical outcomes as well as patient reported outcome measures. This pertinent need is not only restricted to AAV; whilst GC remains imperative in the treatment of a range of nephrological conditions, the narrow therapeutic index means that close observation and monitoring is essential.

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References

1. Jayne D. Evidence-based treatment of systemic vasculitis. Rheumatology [Internet]. 2000 Jun 1;39(6):585–95. Available from: https://doi.org/10.1093/rheumatology/39.6.585
2. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis. 2009 Mar;68(3):310–7.
3. Walsh M, Merkel PA, Peh C-A, Szpirt WM, Puéchal X, Fujimoto S, et al. Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. N Engl J Med [Internet]. 2020 Feb 12;382(7):622–31. Available from: https://doi.org/10.1056/NEJMoa1803537
4. Jayne DRW, Merkel PA, Schall TJ, Bekker P. Avacopan for the Treatment of ANCA-Associated Vasculitis. N Engl J Med [Internet]. 2021;384(7):599–609. Available from: https://doi.org/10.1056/NEJMoa2023386
5. Robson J, Doll H, Suppiah R, Flossmann O, Harper L, Höglund P, et al. Glucocorticoid treatment and damage in the anti-neutrophil cytoplasm antibody-associated vasculitides: long-term data from the European Vasculitis Study Group trials. Rheumatology (Oxford). 2014 Mar;54(3):471–81.
6. Miloslavsky EM, Naden RP, Bijlsma JWJ, Brogan PA, Brown ES, Brunetta P, et al. Development of a Glucocorticoid Toxicity Index (GTI) using multicriteria decision analysis. Ann Rheum Dis. 2017 Mar;76(3):543–6.
7. Sarnes E, Crofford L, Watson M, Dennis G, Kan H, Bass D. Incidence and US costs of corticosteroid-associated adverse events: a systematic literature review. Clin Ther. 2011 Oct;33(10):1413–32.
8. BOLLET AJ, BLACK R, BUNIM JJ. Major undesirable side-effects resulting from prednisolone and prednisone. J Am Med Assoc. 1955 Jun;158(6):459–63.
9. Robson J, Doll H, Suppiah R, Flossmann O, Harper L, Höglund P, et al. Damage in the anca-associated vasculitides: long-term data from the European vasculitis study group (EUVAS) therapeutic trials. Ann Rheum Dis. 2013 Jan;74(1):177–84.
10. McGovern D, Williams SP, Parsons K, Farrah TE, Gallacher PJ, Miller-Hodges E, et al. Long-term outcomes in elderly patients with ANCA-associated vasculitis. Rheumatology [Internet]. 2020 May 1;59(5):1076–83. Available from: https://doi.org/10.1093/rheumatology/kez388
11. Morris A, Geetha D. PEXIVAS challenges current ANCA-associated vasculitis therapy.

Nat Rev Nephrol [Internet]. 2020;16(7):373–4. Available from: https://doi.org/10.1038/s41581-020-0269-6
12. El-Faramawi M, Rohr N, Jespersen B. Steroid-free immunosuppression after renal transplantation—long-term experience from a single centre. Nephrol Dial Transplant [Internet]. 2006 Jul 1;21(7):1966–73. Available from: https://doi.org/10.1093/ndt/gfl131
13. Kasiske BL, Chakkera HA, Louis TA, Ma JZ. A meta-analysis of immunosuppression withdrawal trials in renal transplantation. J Am Soc Nephrol. 2000 Oct;11(10):1910–7.
14. van der Goes MC, Jacobs JWG, Boers M, Andrews T, Blom-Bakkers MAM, Buttgereit F, et al. Monitoring adverse events of low-dose glucocorticoid therapy: EULAR recommendations for clinical trials and daily practice. Ann Rheum Dis. 2010 Nov;69(11):1913–9.
15. Exley AR, Carruthers DM, Luqmani RA, Kitas GD, Gordon C, Janssen BA, et al. Damage occurs early in systemic vasculitis and is an index of outcome. QJM. 1997 Jun;90(6):391–9.
16. McDowell PJ, Stone J, Honeyford K, Dunn L, Logan RJ, Butler CA, et al. Evaluation of the steroid sparing effects of Mepolizumab using the Glucocorticoid Toxicity Index. Eur Respir J [Internet]. 2019 Sep 28;54(suppl 63):PA2513. Available from: http://erj.ersjournals.com/content/54/suppl_63/PA2513.abstract
17. McDowell PJ, Stone JH, Zhang Y, Honeyford K, Dunn L, Logan RJ, et al. Quantification of Glucocorticoid-Associated Morbidity in Severe Asthma Using the Glucocorticoid Toxicity Index. J Allergy Clin Immunol Pract [Internet]. 2020; Available from: http://www.sciencedirect.com/science/article/pii/S2213219820308643
18. Chanouzas D, McGregor JAG, Nightingale P, Salama AD, Szpirt WM, Basu N, et al. Intravenous pulse methylprednisolone for induction of remission in severe ANCA associated Vasculitis: a multi-center retrospective cohort study. BMC Nephrol [Internet]. 2019;20(1):58. Available from: https://doi.org/10.1186/s12882-019-1226-0
19. Jayne DRW, Bruchfeld AN, Harper L, Schaier M, Venning MC, Hamilton P, et al. Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis. J Am Soc Nephrol [Internet]. 2017 Sep 1;28(9):2756 LP – 2767. Available from: http://jasn.asnjournals.org/content/28/9/2756.abstract
20. Merkel PA, Jayne DR, Wang C, Hillson J, Bekker P. Evaluation of the Safety and Efficacy of Avacopan, a C5a Receptor Inhibitor, in Patients With Antineutrophil Cytoplasmic Antibody-Associated Vasculitis Treated Concomitantly With Rituximab or Cyclophosphamide/Azathioprine: Protocol for a Randomized, Doub. JMIR Res Protoc. 2020 Apr;9(4):e16664.
21. Stevens A, Ray DW, Zeggini E, John S, Richards HL, Griffiths CEM, et al. Glucocorticoid Sensitivity Is Determined by a Specific Glucocorticoid Receptor Haplotype. J Clin Endocrinol Metab [Internet]. 2004 Feb 1;89(2):892–7. Available from: https://doi.org/10.1210/jc.2003-031235
22. Schijvens AM, Ter Heine R, de Wildt SN, Schreuder MF. Pharmacology and pharmacogenetics of prednisone and prednisolone in patients with nephrotic syndrome. Pediatr Nephrol. 2019 Mar;34(3):389–403.

Tables

Table 1: The Glucocorticoid Toxicity Index is made up of a composite and specific list relating to glucocorticoid toxicity (6). The composite list includes features of GC toxicity that are weighted and given numerical scores. The specific list includes adverse features of GC treatment but considered significant but are not given a numerical score. Scores can range from - 36 to 439 with increasing scores relating to an increase in GC toxicity burden and negative scores reflecting an improvement in toxicity (16).

Composite GTI	Item weight	Specific List
BMI		
Improvement in BMI	–8	Major increase in BMI
No change in BMI	0	
Moderate increase in BMI	21	
Major increase in BMI	36	
Glucose tolerance		
Improvement in glucose tolerance	-8	Diabetic retinopathy
No change in glucose tolerance	0	Diabetic nephropathy
Worsening of glucose tolerance	32	Diabetic neuropathy
Worsening of glucose tolerance despite treatment	44	
Blood pressure		
Improvement in blood pressure	−10	Hypertensive emergency
No change in blood pressure	0	Posterior reversible encephalopathy syndrome
Worsening hypertension	19	
Worsening hypertension despite treatment	44	
Lipids		
Improvement in lipids	-9	
No change in lipids	0	
Worsening hyperlipidaemia	10	
Worsening hyperlipidaemia despite treatment	30	
Bone density		
Improvement in bone density	-1	Major decrease in bone density
No change in bone density	0	Insufficiency fracture
Decrease in bone density	29	
Steroid myopathy		
No steroid myopathy	0	Severe steroid myopathy
Mild steroid myopathy	9	
Moderate steroid myopathy or greater	63	
Skin Toxicity		
No skin toxicity	0	Severe skin toxicity

Mild skin toxicity	8	
Moderate skin toxicity or greater	26	
Neuropsychiatric toxicity		
No neuropsychiatric symptoms	0	Psychosis
Mild neuropsychiatric symptoms	11	GC-induced violence
Moderate neuropsychiatric symptoms or greater	74	Other severe neuropsychiatric symptoms
Infection		
No significant infection	0	Grade IV infection
Oral/vaginal candidiasis or uncomplicated zoster	19	Grade V infection
Grade III infection or greater	93	
Endocrine		Adrenal insufficiency
Gastrointestinal		
		Perforation, Peptic ulcer disease
Musculoskeletal		
		Avascular necrosis, Tendon rupture
Ocular		
		Central serous retinopathy, intraocular pressure elevation, posterior subcapsular cataract.

Body mass index (BMI), Glucocorticoid (GC) Glucocorticoid Toxicity Index (GTI).

Table 2: Shows the different demographics between PR3 and MPO antibody positive vasculitis patients. The table shows the induction treatment, relapse and mortality results associated with each cohort. Cumulative steroid doses are demonstrated as median cumulative doses with IQR in milligrams (mg). In addition, the number of patients suffering for GC related toxicity at separate time intervals are also shown. Percentages of patients scoring for features of GC toxicity as per the composite list in the glucocorticoid Toxicity Index are presented. All percentages are calculated based on the number of patients alive at each time point.

	Total (n=43)	PR3 (n=19)	MPO (n=24)
Age, years (SD)	65.9 (± 11.06)	58.8 (± 10.75)	71.6 (± 7.97)
Sex (M:F)	20:23	9:10	11:13
eGFR at diagnosis (Median, IQR), ml/min	18 (10.5-27.5)	19 (9-28)	18 (12.5-26.3)
Induction Treatment			
Plasma Exchange	12	8	4
IV Methylprednisolone	16	7	9
Cyclophosphamide	39	17	22
Rituximab	4	2	2
Cumulative steroid dose, mg (median, IQR)			
1 month	1260 (1032.5- 2380)	1365 (1032.5-2487.5)	1155 (1042-2115)
6 months	3870 (2826.3 – 4412.5)	4060 (3432.5 – 4502.5)	3360 (2795-4200)
1 year	4970 (4000-5555)	5247 (4660-5587.5)	4340 (3698.8-5357.5)
2 years	6795 (5092.5-7724)	7072 (6485-7856.5)	5291.3 (4678.5-7337.8)
4 years	9072 (5565-11126)	9330.5 (8121.8-11109.5)	5665 (5223-11407.5)
Number of patients scoring on the composite GTI list (%)			
1 month	3 (7.0)	1 (5.3)	2 (8.3)
6 months	14 (35)	7 (36.8)	7 (32)
1 year	20 (51.3)	11 (57.9)	9 (42.9)
2 years	26 (66.7)	14 (73.7)	13 (61.9)
4 years	27 (71.1)	14 (73.7)	13 (65)
Relapsed disease (n)	8	5	3
ESRF (n)	2	2	0
Mortality (n)	5	0	5

Proteinase 3 antibodies (PR3), Myeloperoxidase antibodies (MPO), Male (M), Female (F), estimated glomerular filtration rate, ml/min/1.73m^2 (eGFR), End Stage Renal Failure (ESRF).

Figures

Figure 1: Shows the cumulative GC dose and GTI scores of individual patients at the end of the study period. The graph shows that at the 4 year follow up, for those still included in the study, a patient with a GTI score of over 60 had received over 9000mg of glucocorticoids (with the exception of one patient).

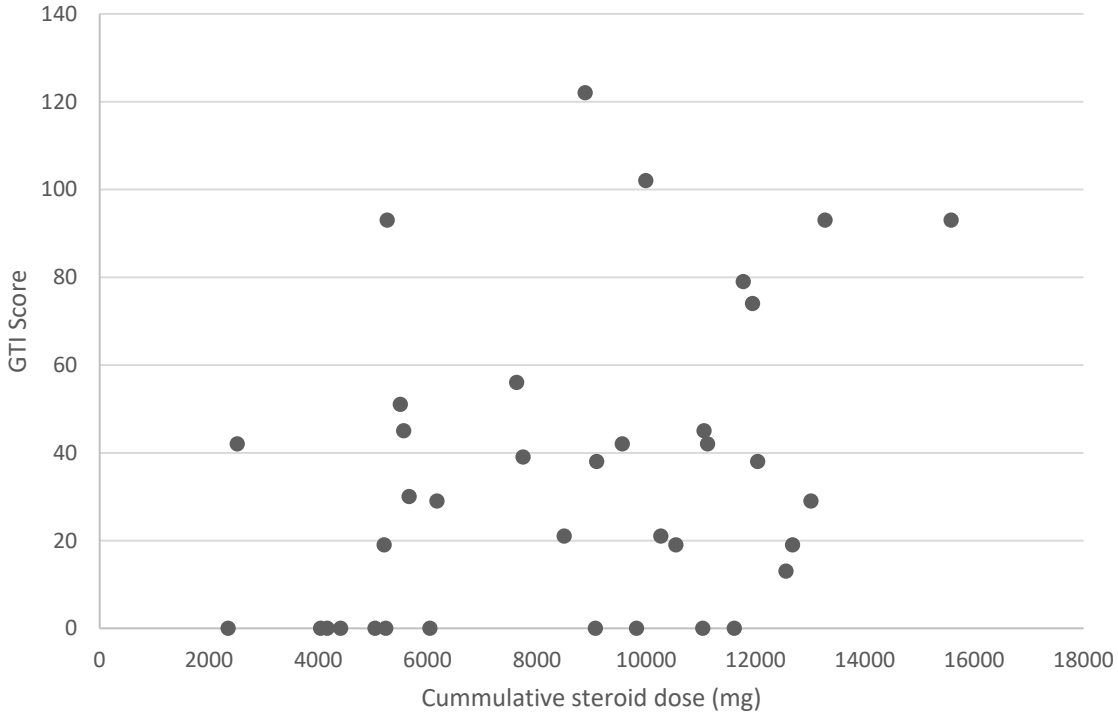
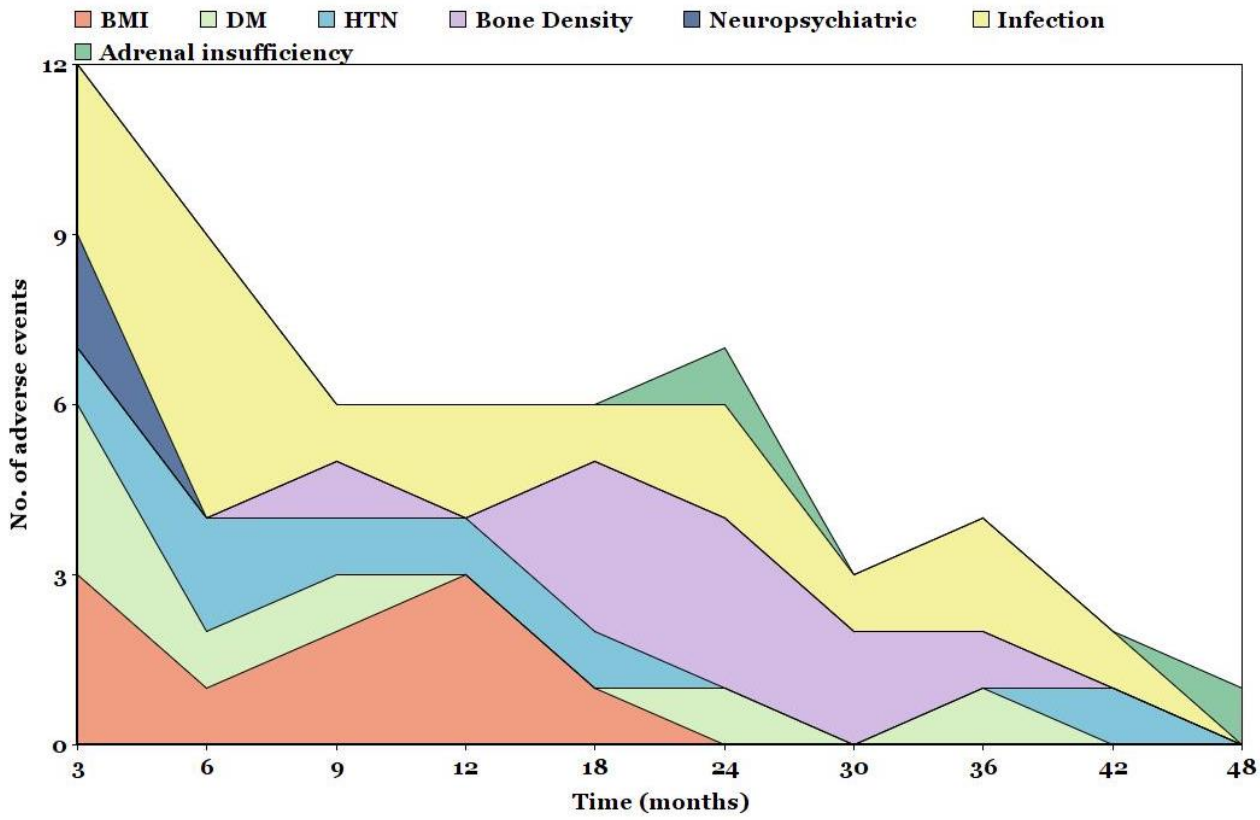
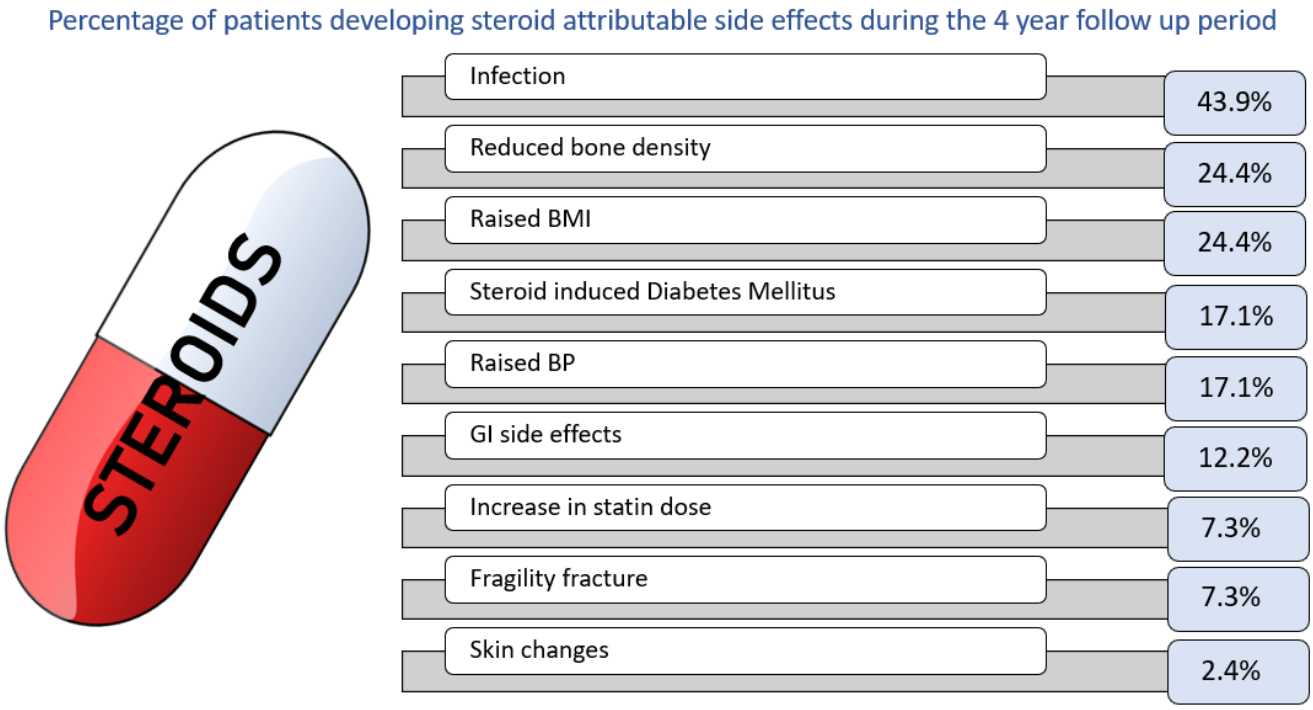


Figure 2: Shows the number of adverse events relating to each category of the glucocorticoid toxicity index over the 48 month follow up period. Each adverse event is scored once and the graph shows the distribution of onset for each adverse feature. The graph shows the number of infections was highest in the first few months and continued throughout the follow up period. Neuropsychiatric presentations occurred early in GC treatment in contrast to adrenal insufficiency which appeared to presented later, typically after 18months of GC treatment.



Body mass index (BMI), diabetes mellitus (DM), hypertension (HTN)

Figure 3: Shows the percentage of adverse effects related to glucocorticoid treatment within our cohort of patients over the 4 year follow up period. Changes in BMI were determined by increases in weight of over 5kg, raised blood pressure was assessed based on a rise of over 20mmHg from baseline or needing up titration of antihypertensive medications to keep BP in range. Infections included anything from oral thrush to sepsis as explained in the composite GTI list.



Body mass index (BMI), Blood pressure (BP), Gastrointestinal (GI) side effects include gastritis and peptic ulcer disease.