

Intravenous Glucocorticoid Pulse Therapy in Active, NSAID Refractory Axial Ankylosing Spondylitis: A Retrospective Analysis Spanning 12 Months

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Received date: February 01, 2018; Accepted date: February 13, 2018; Published date: February 20, 2018

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Abstract

Objective: High dose intravenous glucocorticoid (IVGC) pulse therapy is known to effectively reduce inflammatory signs and symptoms in patients with active inflammatory conditions. However, the efficacy of IVGC in ankylosing spondylitis (AS) is not clearly established.

Methods: We performed a retrospective analysis with repeated measurements including patients with active, NSAID refractory axial AS (n=15) who underwent high dose IVGC pulse therapy. Parameters of clinical and humoral disease activity were compared to active AS patients (n=14) under continuous anti-TNF treatment. Patients were seen every 3 months and followed up for a total period of 12 months.

Results: Both IVGC pulse and anti-TNF therapy lead to a significant and sustained reduction of the mean bath ankylosing spondylitis disease activity index (BASDAI 7.4 ± 1.5 at baseline vs. 5.4 ± 2.1 at 12 months in the pulse group and 6.9 ± 1.2 at baseline vs. 5.0 ± 2.7 at 12 months in the anti-TNF group, p<0.001), CRP (p=0.018), ESR (p=0.028), morning stiffness (p<0.001), and finger-to-floor-distance (p=0.001; within group comparison).

Conclusions: Patients with active axial AS treated with one IVGC pulse show a substantial decrease in disease activity over a period of 12 months in this retrospective analysis.

Key words:

Spondyloarthritis; Ankylosing spondylitis; Glucocorticoids; IVGC pulse

Introduction

High dose intravenous glucocorticoid (IVGC) pulse therapy is a therapeutic option rapidly reducing acute inflammatory signs and symptoms in active rheumatic disorders such as giant cell arteritis, rheumatoid arthritis, and systemic lupus erythematosus [1-3]. However, the positive effects of this treatment are less clear in ankylosing spondylitis (AS) [4]. So far, only few small, uncontrolled studies suggest that IVGC has beneficial effects in AS [5-10]. One published small randomised, placebo-controlled study showed some positive effects for oral prednisolone (50 mg daily over 2 weeks) in active AS patients [11].

We performed a retrospective analysis with repeated measurements (every 3 months up to 12 months) including patients with active AS refractory to NSAID treatment who underwent IVGC pulse therapy and compared them to active AS patients in whom an anti-TNF treatment was initiated. IVGC treatment reduced signs and symptoms over a period of up to 12 months.

Methods

Patients analysed in this study were selected out of a total of 219 spondyloarthritis patients who were refractory to NSAID treatment and were thus submitted to IVGC pulse treatment in our clinic (Figure 1).

Out of these 219 patients, 99 active AS patients were identified, however, only 67 AS patients could be followed up to 12 months; among these 67 patients, the majority (n=38.57 %) had a predominant axial disease. The remaining 29 patients with a predominant peripheral manifestation were excluded from the analysis. Finally, 15 patients with active AS receiving high dose IVGC were selected for the analysis (Figure 1). As comparison, we analysed 14 patients with active axial AS also refractory to NSAID treatment in which an anti-TNF treatment was initiated. All 29 patients fulfilled the following criteria:

- Diagnosis of AS according to the modified New York criteria [12],
- Active disease, i.e. BASDAI ≥ 4 despite treatment with two or more NSAIDs in maximum doses given over a period of 8 weeks prior to the intervention, and
- follow-up for 12 months with regular re-evaluations in our out-patient unit at the following time points: directly after treatment intervention (i.e. the last day of or the day after the IVGC pulse

treatment; however, this time point was only available in the IVGC pulse group and is not depicted in (Figure 2), and thereafter at intervals of 3 months up to 12 months.

d) No more than 2 changes of additional NSAID treatment during the observation period.

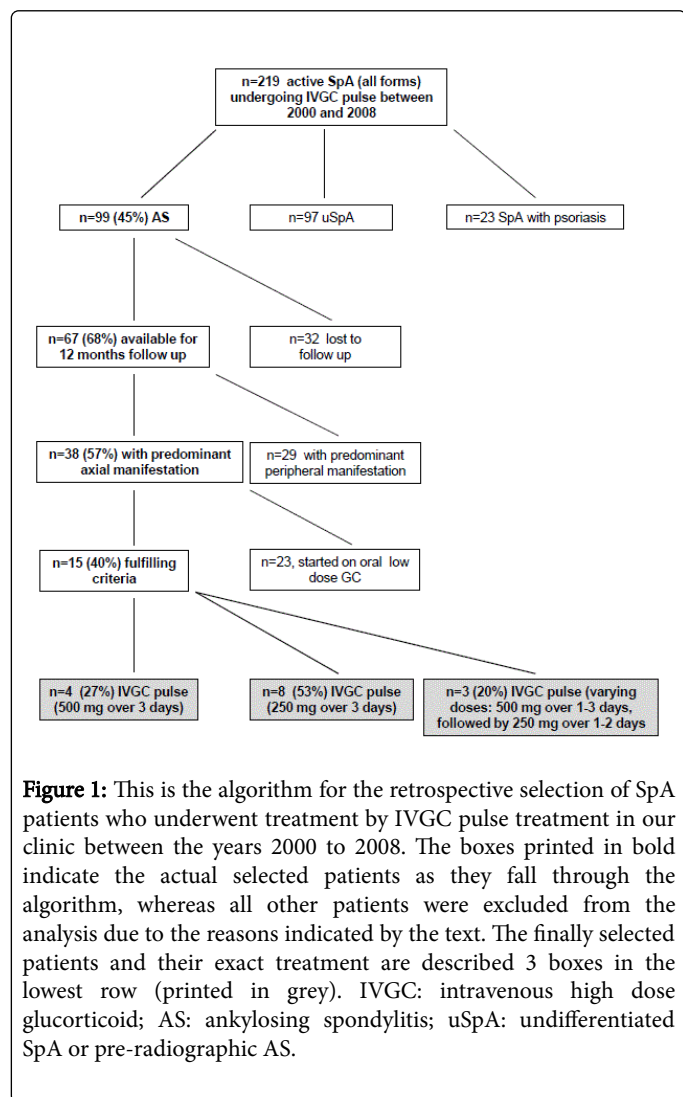


Figure 1: This is the algorithm for the retrospective selection of SpA patients who underwent treatment by IVGC pulse treatment in our clinic between the years 2000 to 2008. The boxes printed in bold indicate the actual selected patients as they fall through the algorithm, whereas all other patients were excluded from the analysis due to the reasons indicated by the text. The finally selected patients and their exact treatment are described 3 boxes in the lowest row (printed in grey). IVGC: intravenous high dose glucocorticoid; AS: ankylosing spondylitis; uSpA: undifferentiated SpA or pre-radiographic AS.

Clinical characteristics as well as parameters of systemic inflammation and spinal mobility of all 29 patients at baseline are summarized in Table 1.

Epidemiology	IVGC pulse group	TNFi group
no of patients (n)	15	14
female gender (%)	1 (7%)	10 (74%)
mean age in y. (mean ± SD)	47 ± 12	45 ± 12
DD in years (mean ± SD)	11 ± 11.5	6 ± 6.3
Clinical parameters	IVGC pulse group	TNFi group
BASDAI (mean ± SD)	7.4 ± 1.5	6.9 ± 1.2
MST in min. (mean ± SD)	138 ± 94	137 ± 31

FFD in cm (mean ± SD)	36 ± 15.6	20 ± 12
CE in cm (mean ± SD)	4.4 ± 2.7	5.8 ± 2
Ott in cm (mean ± SD)	2 ± 1.7	3 ± 1.3
Schober in cm (mean ± SD)	2 ± 1.1	4 ± 1.3
Laboratory parameters	IVGC pulse group	TNFi group
ESR in mm/h (mean ± SD)	15 ± 11	15 ± 17
CRP in mg/l (mean ± SD)	28 ± 34.2	12 ± 12
HLA-B27 pos. (%)	9 (60%)	9 (64%)

Table 1: This table shows the clinical data at baseline of both the IVGC pulse as well as the TNFi group (mean values ± SD). There were no statistical differences between the two groups. IVGC, intravenous glucocorticoid; TNFi, TNF inhibitor; DD, disease duration; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; MST, morning stiffness; FFD, finger-to-floor-distance; CE, chest expansion; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

The 15 patients in the IVGC pulse treatment group received 250 to 500 mg/d iv prednisolone for 3 to a maximum of 5 consecutive days (Figure 1, please see 3 boxes in last row). NSAID medication was stopped during the IVGC pulse treatment to avoid gastrointestinal toxicity, but was reinitiated after the pulse. The other group of patients (14/29, 48%) was started on TNF-antagonists, i.e. infliximab, etanercept, or adalimumab according to the approval status in Germany at that time.

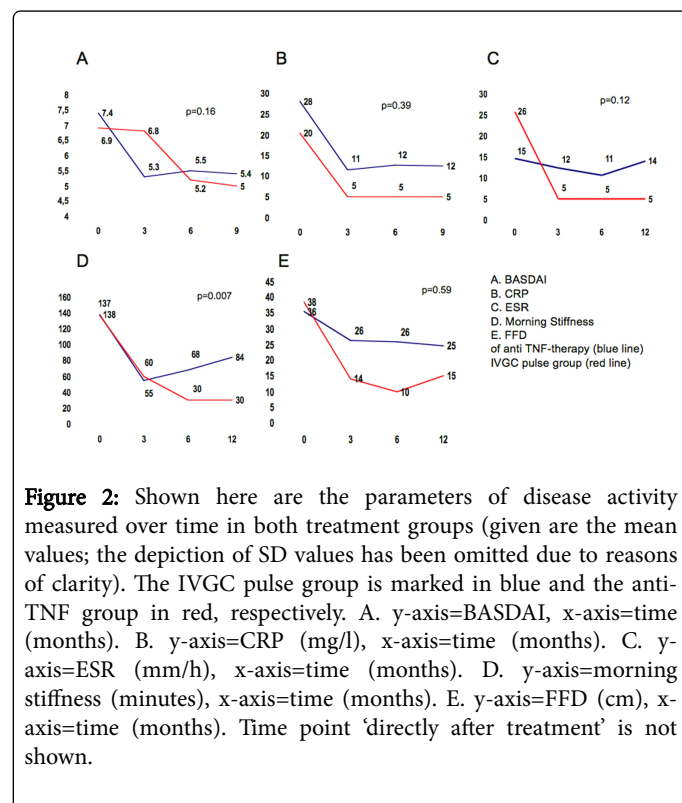


Figure 2: Shown here are the parameters of disease activity measured over time in both treatment groups (given are the mean values; the depiction of SD values has been omitted due to reasons of clarity). The IVGC pulse group is marked in blue and the anti-TNF group in red, respectively. A. y-axis=BASDAI, x-axis=time (months). B. y-axis=CRP (mg/l), x-axis=time (months). C. y-axis=ESR (mm/h), x-axis=time (months). D. y-axis=morning stiffness (minutes), x-axis=time (months). E. y-axis=FFD (cm), x-axis=time (months). Time point 'directly after treatment' is not shown.

Patients had not received oral or IVGC therapy before, during or after the observed period. During follow-up, both groups received NSAID treatment on demand but no oral GC treatment.

Potential toxicity problems associated with the pharmacological treatment such as onset or worsening of hypertension, diabetes, mental disorders, or infections were documented. Furthermore, the patients were contacted by a questionnaire asking for diagnoses of osteoporosis or any fractures possibly associated with such a condition spanning a period of up to 6 years after the IVGC pulse therapy was performed.

Within groups, patients were analysed using the Wilcoxon-Signed Rank test. For comparisons between both groups, we used analysis of variance (ANOVA) including the Mauchly test with Greenhouse-Geisser correction applied for testing sphericity of both groups.

This study was approved by the local ethical committee.

Results

Demographics and clinical data of both treatment groups at baseline were similar. However, there was a clear difference in the female:male ratio as well as the disease duration, the spinal mobility (finger to floor-distance and Schober's test), and the CRP values (Table 1). In the IVGC pulse group, disease activity decreased rapidly and was sustained in the majority of parameters such as CRP, BASDAI and FFD for up to 12 months (Figure 2).

In particular, the mean BASDAI decreased from 7.4 (\pm 1.5) at baseline to 3.9 (\pm 2.4) directly after treatment ($p < 0.001$, data not shown), to 5.3 (\pm 1.8) at 3 months ($p < 0.001$), to 5.5 (\pm 1.8) at 6 months ($p < 0.001$), and to 5.4 at 12 months ($p < 0.001$, which was still significant after Bonferroni adjustment. Similar data were obtained for patients receiving anti-TNF agents (Figure 2). In addition, the humoral disease activity measured by ESR and CRP decreased in both the IVGC pulse as well as the anti-TNF group at 3 months (15,3 mm, 12.4 mg/l and 9.8 mm, 7.4 mg/l, respectively; ESR $p = 0.048$, CRP $p = 0.26$) and remained on low levels at 6 months (6.6 mm, 8 mg/l, respectively; ESR $p = 0.033$, CRP $p = 0.046$), as well as at 12 months (6,4 mm, 5 mg/l; ESR $p = 0.019$, CRP $p = 0.024$; Figure 2). 8/10 patients with increased CRP levels in the pulse group revealed normal values after 3 months, as did 6/10 patients after 3 months, 3/10 patients after 6 months, and 2/10 patients after 12 months. ESR and CRP values did not increase during the observation period in both groups.

The mean spinal morning stiffness was 138 min. in the IVGC pulse group and 77 min. in the anti-TNF group. These values were reduced to 55 min after 3 months, to 68 after 6 months, and to 84 min. after 12 months ($p < 0.001$) at all time points (Figure 2).

Among the parameters of spinal mobility, the finger to floor-distance (FFD) and the Schober's test had significantly increased in the pulse group at all documented time points when compared to baseline ($p < 0.01$). However, there were no significant changes of chest expansion and the Ott's test (data not shown). Of note, the FFD was the only parameter showing a clear improvement in the anti-TNF group as compared to the pulse group after 12 months (14.5 cm in anti-TNF vs. 24.47 cm in the pulse group, within group comparison).

There were no severe adverse events in the two treatment groups. The moderate adverse events in the pulse group included an asymptomatic increase of the systolic blood pressure from normal values of up to 160 mmHg in two patients. In the two patients, antihypertensive treatment with oral amlodipin 5 mg/d was initiated

leading to normal values within 24 hours. There was also a transient increase in blood sugar levels in 12 patients, but hyperglycaemia was moderate and fully reversible in all patients and did not require insulin treatment. In addition, several mild serum potassium and sodium abnormalities were observed without any clinical relevance. None of the patients contacted by questionnaire reported avascular osteonecrosis and osteoporosis within the first year. However, one patient developed a humerus fracture after a minimal trauma 3 years after IVGC treatment and another patient in the pulse group was diagnosed by a spontaneous fracture 2 years after IVGC treatment.

Discussion

The therapeutic potential for AS has enormously increased due to the approval of biologic agents in active and NSAID refractory disease. However, TNF- or IL17-antagonists prove efficacious in only a proportion of patients and do not entirely inhibit structural damage; in addition, they can lead to potentially severe short and long term side effects and are very costly. One therapeutic alternative might be a pulse of high dose glucocorticoids (IVGC), but clinical data are scarce. A limited number of studies [5-10], all but one being published in the pre anti-TNF era, show at least partially positive effects of IVGC pulse therapies as opposed to low dose oral GC treatment; a phenomenon possibly associated with the various degrees of GC dissolving into cell membranes [13,14]. Nevertheless, there is one controlled study on oral prednisolone that showed a mean BASDAI improvement in the 50 mg/d group given over 2 weeks but does not follow up patients beyond that relatively short period of time [11].

Our retrospective analysis is the only study that includes the BASDAI, observes patients over a 12 months period, and compares steroid vs anti-TNF treatment. Our data show comparable therapeutic effects of high dose IVGC and anti-TNF treatment in active AS patients. The positive effects in regard to both clinical and humoral disease activity as well as spinal mobility are sustained over a 12 months period not only in the anti-TNF group but interestingly also in the IVGC pulse group.

In particular, the sustained long term effects exerted by a single IVGC pulse extend the former observation of improvement of signs and symptoms for up to 6 and 10 months, respectively, as reported by previous studies [5,8]. These findings have prompted us to carefully analyze the co-medication and any other treatment in the two groups prior to and following the initial treatment, i.e. during the 12 months observation period, in order to rule out relevant differences. These differences could not be observed. However, there were slight but not significant differences in regard to the baseline characteristics of the two groups (i.e. a slightly higher disease activity in the IVGC group; see Table 1).

IVGC and biologic agents alike are known to have potent anti-inflammatory effects such as the inhibition of innate immune cells and the down regulation of cytokines such as IL-1, IL-2, IL-6, IL-8, IL-17, TNF, and GM-CSF due to the blocking of the two pivotal transcription factors NF- κ B and AP-1 [14,15]. This is most likely one major explanation for the positive clinical effects of the high dose GC pulse treatment.

Apart from this possible explanation for the positive clinical effects of the high dose GC pulse treatment, the natural course of the disease and to some extent the treatment induced regression to the mean also contributed to the favorable one year outcome in these AS patients.

The limitations of this study should be clearly mentioned here: one is the retrospective analysis which is not allowing any randomization; another point is the comparison of different patient groups treated at different time periods. There also might be a bias due to the exclusion of patients with more than 2 NSAID changes. In addition, the two treatment groups had to fulfill the above mentioned inclusion criteria focusing on a similar, i.e. comparably high disease activity but were not matched in regard to age or gender. Besides, we did not analyze extra-articular manifestations.

The toxicity problems associated with high dose IVGC pulse therapies in general are mostly foreseeable and manageable by experienced personnel. In general, the adverse events observed here were all mild to moderate and comparable with the ones reported in an earlier study that closely monitored any adverse events of an IVGC pulse therapy [16]. In particular, we did not observe potential long-term side effects including avascular osteonecrosis, induction of diabetes, or adrenal gland insufficiency in the following year, i.e. two years after the initial treatment. Within two to three years after the GC pulse, no severe complications had been documented. One long term problem clearly is the glucocorticoid induced reduction of bone mineral density leading to fractures, which was observed in a small portion of our patients.

Conclusion

Taken together, IVGC pulse treatment has positive therapeutic effects in NSAID refractory patients with active ankylosing spondylitis as measured by parameters of disease activity and improvement of spinal mobility. Of note, the suppression of disease activity was sustained in most parameters over an observation period of 12 months indicating that this treatment may be at least an additional alternative reducing effectively and safely the inflammatory burden in AS; in particular, it might be a short-term treatment such as bridging of flares in highly active AS patients not responding to a previous conventional treatment. This study lends support to further investigating the efficacy of single and/or repeated IVGC pulse treatment, possibly in combination with biologic agents, in prospective studies.

Competing Interests

The authors state that there are no competing interests.

Funding

This work has been supported by the Competence Network Rheumatology, Berlin.

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