Post hoc analysis of the Exenatide-PD trial – factors that predict response

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Abstract

Exenatide, a glucagon-like peptide-1 agonist and a licensed treatment for Type 2 diabetes significantly reduced the deterioration in motor symptoms in patients with Parkinson’s disease in a recent randomised, placebo-controlled trial. In addition, there were trends favouring the exenatide group in assessments of non-motor symptoms, cognition and quality of life. The aim of this exploratory post-hoc analysis was to generate new hypotheses regarding (1) whether candidate baseline factors might predict the magnitude of response to exenatide and (2) whether the beneficial effects of exenatide reported for the overall population are consistent in various subgroups of patients.

Univariate and multivariate analyses were conducted to determine possible predictors of motor response to exenatide in this cohort. Potential treatment by subgroup interactions for changes in; motor severity, non-motor symptoms, cognition and quality of life after 48 weeks treatment with exenatide were evaluated among post-hoc subgroups defined by age, motor phenotype, disease duration, disease severity, BMI and insulin resistance.

In the subgroup analyses, exenatide once-weekly was associated with broadly improved outcome measures assessing motor severity, non-motor symptoms, cognition and quality of life across all subgroups, however tremor-dominant phenotype and lower MDS-UPDRS Part 2 scores predicted greatest motor response to exenatide and there was an indication that patients with older age of onset and disease duration over 10 years responded less well.

While patients with a wide range of demographic and clinical factors can potentially benefit from exenatide once-weekly, these data support an emphasis towards recruitment of patients at earlier stages of the disease in future planned clinical trials of GLP-1 receptor agonists in PD.
Preface

Tom Isaacs was a driving force behind much of the basic science and clinical research regarding exenatide and other GLP1 receptor agonists as potential repurposed treatments for Parkinson’s disease. He personally represented patient opinion on the Exenatide-PD Phase 2 trial Steering committee. He was greatly interested in if and how new treatments might be more suitable for one patient rather than another and was very keen that we explored the results of this trial in depth to learn what we could about potential different responses to exenatide in different people with PD.

Introduction

Parkinson’s disease (PD) is a progressive neurodegenerative disorder characterised by the loss of dopaminergic neurons in the substantia nigra pars compacta accompanied by the development of motor and non-motor symptoms. Although there are a number of effective symptomatic therapies targeting dopaminergic signalling pathways, none of these has been shown to affect the course of disease progression. Exenatide, a gluacagon-like peptide-1 (GLP-1) agonist used in the treatment of Type 2 diabetes, was recently studied for potential disease-modifying effects in a randomised, placebo-controlled clinical trial in patients with moderate stage Parkinson’s disease (Athauda et al., 2017). The primary outcome was met and, in line with the earlier open label trial, patients using exenatide exhibited statistically significant improvements in motor function compared with those on placebo (measured after overnight dopaminergic withdrawal) at 48 weeks (4.3 points; 95%CI −7.1 to −1.6; p=0.0026), sustained after a 12-week washout (−3.5 points; 95%CI −6.7 to −0.3; p=0.0318). These results need to be replicated in larger patient numbers and their clinical significance assessed though longer term exposure to properly interpret the cumulative impact of this intervention. Regarding secondary outcomes, analysis of results evaluating quality of life (assessed by the PDQ-39), cognition (assessed by the Mattis-DRS2) and non-motor symptoms (assessed by the NMSS)
indicated trends favouring the exenatide group but these differences did not reach thresholds for statistical significance.

It is well recognised that treatment effects may not be homogenous across study populations (Tanniou et al., 2016), and this applies particularly to PD patients, with variability in response to conventional treatments being a common finding. This treatment response variability may relate to individual, disease- or drug-specific factors (Nomoto et al., 2009) and an appropriately conducted post-hoc analysis may help to identify these factors and aid in future trial design (Devonshire et al., 2012). A post-hoc analysis of the effects of exenatide on non-motor symptoms has previously been reported (REF) and both this and the current analysis were performed with the objective of helping generate hypotheses as part of the future planning of exenatide trials in PD.

We conducted a post hoc exploratory analysis using two main techniques. The first examined baseline demographic and clinical characteristics, to identify factors associated with greatest response that may thus allow one to predict which future patients would benefit from exenatide, as well as whether an early response might predict the longer term response. Furthermore, we used the minimal clinically important difference in MDS-UPDRS score (an improvement of 3.25 points) to classify patients into high-responders and low-responders to determine which baseline characteristics predicted which patients gained the greatest magnitude of improvement. Our second technique was to perform an analysis in predefined PD subgroups to examine the heterogeneity of treatment effects on motor severity, non-motor symptoms, cognition and quality of life, to generate new hypotheses and provide useful information for patient selection / stratification in future trials. Patient subgroups of interest were defined post hoc based but based on observed effects in subgroups reported in previous studies and/or with strong biological reasoning. These subgroups included demographic factors (age, age of symptom onset), disease characteristics (severity of PD, motor phenotype, disease duration, presence of mild cognitive impairment) and metabolic factors (insulin resistance, obesity).
Methods

Study design

This was a post-hoc analysis of a 60 week, randomised, placebo-controlled trial that evaluated the efficacy of exenatide as a potential disease modifying agent in patients with moderate stage PD (Athauda et al., 2017). The study is registered at ClinicalTrials.gov (NCT01971242). Patients were randomly assigned (1:1) to receive subcutaneous injections of exenatide 2mg once-weekly or matched placebo for 48 weeks in addition to their regular medication. Patients and investigators were blinded to treatment allocation. The primary outcome was the adjusted difference in the Movement-Disorders-Society-Unified-Parkinson’s-Disease-Rating-Scale (MDS-UPDRS) motor subscale (Part 3) in the practically defined OFF medication state at 60 weeks (i.e. following a 12 week exenatide washout period). Full details of the trial design and methods were previously reported (Athauda et al., 2017). This trial was approved by the Brent NHS Research Ethics Committee, London. All patients provided written informed consent.

Patients

Eligible patients were men and women aged between 25 and 75 years old with idiopathic PD based on Queen Square Brain Bank criteria, were on dopaminergic treatment with wearing off phenomena, and were at Hoehn and Yahr stage 2.5 or less when on PD medication. Key exclusion criteria included concurrent dementia (defined as score <120 points on the Mattis-Dementia Rating scale (DRS-2) and patients with Body mass index <18.5. All patients signed a written informed consent before entry into the study.

Post hoc analyses

The first analysis evaluated the predictive relationship between baseline patient disease characteristics / demographics and change in MDS-UPDRS Part 3 OFF scores after 48 weeks of
exenatide treatment (n=31) firstly as continuous univariates then as part of a multivariate analysis. Next, patients were stratified into high responders and low-responders, defined as whether patients had an improvement in the MDS-UPDRS Part 3 OFF score of at least 3.25 points at 48 weeks (accepted as the minimal clinically important difference in the motor examination of the MDS-UPDRS (Horváth et al., 2015) N.B. see also Discussion).

Treatment effects were subsequently investigated by examining the effects of exenatide among putative subgroups (i.e. a categorical analysis) on the four major outcomes of the trial at 48 weeks of treatment namely; motor severity (change in MDS-UPDRS Part 3 off medication); non-motor symptoms (change in Non-motor symptom (NMS) score); quality of life (change in Patient Parkinson's Disease Questionnaire – (PDQ-39) and cognition (change in Mattis-DRS2) assessed in the On medication state. Patient subgroups were defined post hoc but were based on previous knowledge from studies which suggest severity of disease and disease duration may influence progression and response to treatment (Kordower et al., 2013; Reinoso et al., 2015), thus patients were defined at baseline into (1) age (<50 years, 50-64 years, >65 years); (2) age at symptomatic onset (younger than 50 years, 50-59 years, and >60 years) – chosen following a cluster analysis of patients with early PD (Post et al., 2008); (3) predominant motor phenotype (Tremor dominant vs akinetic-rigid); Motor phenotype was determined by dividing each patient’s tremor score (mean of items MDS-UPDRS 2.10, 3.15a, 3.15b, 3.16a, 3.16b, 3.17a, 3.17b, 3.17c, 3.17d, 3.17e, 3.18) by the PIGD score (mean of items MDS-UPDRS 2.12, 2.13, 3.10, 3.11, 3.12). If the resultant ratio is ≥1.15, then the patient is classified with TD; if the ratio is ≤0.90, then the patient is classified with PIGD. If the ratio is between 0.90 and 1.15 the patient is classified as indeterminate (Stebbins et al., 2013). (4) disease duration (<4 years, 4-10 years, >10 years) (Kordower et al., 2013); and (5) presence of mild cognitive impairment (Mattis-DRS2<137) (Pirogovsky et al., 2014). In addition, it is well known that exenatide exerts effects on insulin resistance and obesity and thus patients were also classified according to (6) presence/absence of insulin resistance (defined as HbA1c >39mmol/mol); and (7) obesity (defined as BMI>25.0).
**Statistical analyses**

The change in MDS-UPDRS Part 3 was calculated as the difference in MDS-UPDRS Part 3 scores from baseline to week 48. Linear models were used to examine the univariate and multivariate relationships between baseline demographic, clinical and biological predictors and the change in MDS-UPDRS Part 3 score at 48 weeks (dependent variable). Any variables with univariate associations with p-values <0.20 were considered to be potentially associated with treatment and were included in a multivariate model, and a backwards selection process was used to remove variables individually until all remaining variables were significant at the 0.10 level. A bootstrap resampling procedure with 1000 repetitions to the regression models was applied. Bootstrapping replicates the process of sample generation from an underlying population by drawing samples with replacement from the original data set and is useful as an alternative to parametric estimates when the assumptions of those methods are in doubt due to the small sampling size. Responder and non-responder groups were compared using two-sided t-test and χ2 tests for normally distributed variables and Mann-Whitney tests for non-parametric data. Univariate logistic regression was conducted to identify possible factors for identifying a responder to exenatide treatment at 48 weeks and several multivariate logistic regression models were then developed with responder at 48 weeks as the dependent variable.

To examine the heterogeneity of treatment effects across various subgroups, a test of interaction was conducted. Multiple linear regression of change in MDS UPDRS Part 3 off-medication scores was fitted with change in treatment group, subgroup and the interaction of subgroup and treatment group as independent variables. Baseline values, change in Levodopa equivalent dose were added as possible covariates. This was repeated for other outcome measures. All study analyses were performed using STATA/MP (StataCorp, Version 14.1 MP, College Station, TX, USA) and SPSS (IBM, Version 21.0. Armonk, NY: IBM Corp).
Results

**Post hoc analysis**

*Predicting motor response to exenatide at 48 weeks*

The results of the univariate analysis are presented in Table 1. Baseline characteristics that significantly predicted a favourable response to exenatide were; lower MDS-UPDRS Part 2 scores (p=0.008), and tremor-predominant motor subtype (p=0.013). Predictors with a p value<0.2 were then used in the multivariate analysis, adjusted for baseline MDS-UPDRS Part 3 score. In the multivariate analysis, greater improvement in MDS-UPDRS Part 3 OFF scores from baseline to 48 weeks was again associated with a tremor predominant motor phenotype and lower baseline MDS-UPDRS Part 2 scores (Table 1).

In addition to baseline demographics and disease characteristics, response to exenatide at 12 weeks (as measured by change in MDS-UPDRS Part 3 from baseline to 12 weeks) predicted response to exenatide at 48 weeks, Beta coefficient=0.426 (95%CI 0.10, 0.85); p=0.047.

**Responder analysis**

Of the 31 patients randomised to exenatide treatment, 14 (45%) patients had an improvement of the MDS-UPDRS Part 3 of at least 3.25 points at 48 weeks and were characterised as high responders.

Baseline patient demographics and disease characteristics were generally similar between high responders and low-responders in the exenatide group (Table 2). Patients in the high-responder group were slightly younger, and tended to have overall less disease burden, as shown by a trend in lower numerical scores in the MDS-UPDRS Part 1-3 and NMSS. Of note, there were no patients in the high-responder group that had any postural instability (versus 29% in the low-responders, p=0.048)
or speech difficulties (versus 35%, p=0.021) at baseline. In addition, there were no patients that had disease duration over 10 years in the high-responder group.

Using those clinical variables most strongly associated with change in MDS-UPDRS Part 3 in the univariate analysis (age, motor phenotype, MDS-UPDRS Part 2, MDS-UPDRS Part 4) a logistic regression analysis to predict response produced good discrimination, AUC 0.79 (95%CI 0.62, 0.95; p=0.007), Nagelkerke’s R2 of 0.39 and an acceptable goodness of fit (Hosmer-Lemeshow Chi-Square 11.52; 8 df; p=0.174) in the final risk model (Table 3). Patients with lower MDS-UPDRS Part 2 scores were more likely to have a high-response to exenatide with a trend for those patients with a tremor dominant phenotype to also respond well.

**Subgroup analysis**

Linear regression models identifying significant interactions between subgroups and change in outcome variable at 48 weeks were constructed, allowing for correction for potential confounding variables including baseline variable value, and change in levodopa equivalent dose. For all models, the assumptions of linearity, independence of errors, homoscedasticity and normality of residuals were met. The mean (SEM) and Forest plots for subgroups according to randomisation outcome that were included in the regression models are presented in Figures 1-4.

**Motor effects - change in UPDRS Part 3 score**

Figure 1 shows the subgroup analysis for change in MDS-UPDRS Part 3 scores at 48 weeks from baseline. There was a trend that patients aged over 65 (Beta coefficient=5.785, (95%CI -0.36, 11.93); p=0.065) or patients that developed symptoms after the age of 60 years (Beta coefficient=5.187 (95%CI -0.93, 11.3); p=0.095) had a worse outcome. There were no significant interactions between the treatment group and disease duration, insulin resistance, motor phenotype, presence of MCI or obesity.

**Non-motor symptoms – change in NMS score**
Figure 2 show the subgroup analyses of Change in total Non-motor symptom score at 48 weeks from baseline. There were differential effects of exenatide on NMS, with advantageous effects in patients with a disease duration of less than 4 years Beta coefficient= -17.28 (95%CI -37.46, 2.89); p=0.092 compared with disease duration over 10 years Beta coefficient = 25.21 (95%CI 2.87, 47.56); p=0.028.

Quality of life – change in PDQ-39 score

Figure 3 shows the subgroup analyses of Change in total Parkinson’s disease Questionnaire-39 (PDQ-39) score at 48 weeks from baseline. Patients with a disease duration over 10 years had a worse change in this quality of life health measure Beta coefficient=12.4 (95%CI 1.3, 23.4); p=0.029 and also there was a trend for differential effects in patients diagnosed after the age of 60, Beta coefficient=7.7 (-0.5, 16.0), p=0.067.

Cognitive effects – change in Mattis DRS-2

Figure 4 shows the subgroup analyses of Change in Mattis-DRS2 score at 48 weeks from baseline. There was a significant interaction term with less improvement in the tremor dominant phenotype Beta coefficient= -3.894 (95%CI -7.5, -0.3); p=0.036. There was also a trend to significance for greater improvement in patients defined as obese Beta coefficient= 3.3 (95%CI -0.24, 6.9); p=0.066 and in patients defined as having insulin resistance Beta coefficient=2.5, (95%CI -0.4, 5.4); p=0.094.

Discussion

We have performed an exploratory, hypothesis generating study to evaluate baseline variables that may help inform future studies regarding which PD patients may be predicted to respond best to exenatide and in addition, performed a subgroup analysis of the effects of exenatide versus placebo on motor severity, non-motor symptoms, cognition and quality of life in patient subgroups that participated in the Exenatide-PD phase 2 trial. The overall number of PD patients treated with
Exenatide so far remains small and replication of these results is urgently needed before any clinically relevant decisions are made, however our analyses show that overall, there is a generally consistent effect of exenatide across most subgroups of patients.

Although responder analysis has been recommended as an alternative approach to assessing clinical relevance (FDA Center for Drug Evaluation and Research, 2006), and can help results be more intuitively interpreted than a difference in mean rating scales, it is well known that dichotomization of continuous variables usually results in loss of statistical power and the analysis can often vary considerably depending on the response cut-off chosen (Snapinn & Jiang, 2007). There is no well-recognized definition of what constitutes a “responder” in PD clinical trials but by utilising an accepted cut-off for the minimal clinically important difference in the MDS-UPDRS Part 3 (Horváth et al., 2015), we have attempted to define a high responder as a patient that experience improvements that would be clinically relevant. This said, exenatide is being investigated for its potential disease modifying properties rather than symptomatic ones. If disease-modifying effects are cumulative with longer term exposure to exenatide, then any minimal advantage over placebo might still translate to a clinically important effect over the longer term, and our high-responder cut-off criterion might be unduly strict.

Furthermore, while an appropriately conducted subgroup analysis can help identify patient subgroups in which the treatment has a higher or lower efficacy (Devonshire et al., 2012), the Exenatide-PD trial was not designed or powered to formally test for heterogeneity or trends between subgroups and as such, there are a number of inherent limitations such as the analysis being underpowered, which may be a source of false negative results. In addition, formal adjustment of p values to correct for multiplicity in view of the multiple individual subgroup analyses was not done to avoid rejecting the null hypothesis too readily in such an exploratory analysis (Rothman et al., 2017); this naturally increases the risk of false positive findings and thus, inferences made from this analysis and reported p values should be interpreted with caution, and the data used to inform
on planning of future formal hypothesis testing studies only. Although all subgroups examined in this analysis were defined post hoc, groups of interest were determined based on previous clinical and scientific criteria of interest and are not purely data driven.

The multivariate analysis indicated that in patients treated with exenatide, a greater improvement in MDS-UPDRS Part 3 scores could be predicted by patients with a tremor dominant phenotype and lower MDS-UPDRS Part 2 scores. Patients categorised as high-responders tended to be younger and have lower disease severity as shown by MDS-UPDRS Part 1-3 scores. Logistic regression indicated that for each one point increase in MDS-UPDRS Part 2 score, the odds of being a high-responder to exenatide treatment decrease by 1.17 (p=0.044) while patients with a tremor dominant phenotype were 2.5 times more likely to have a clinically meaningful motor response to exenatide (p=0.086).

Importantly, patients with tremor dominant PD had a disease duration of 9.4 years (SEM 1.5) compared with 5.8 years (SEM 0.6) for patients with the akinetic-rigid phenotype and these differences may have contributed to the findings but despite the heterogeneity of PD, there have been multiple studies suggesting patients with a tremor dominant phenotype have a less aggressive disease course, with less pathological burden and a lower degree of dopaminergic denervation (Selikhova et al., 2009; Eggers et al., 2012; Huertas et al., 2017). This fact, taken together with our observation that patients with lower disability as rated by lower MDS-UPDRS Part 2 scores, may indicate that patients with less aggressive, milder disease load may have more compensatory mechanisms for exenatide to exert any disease modifying effects.

Considered separately was the change in MDS-UPDRS Part 3 at 12 weeks, which could predict which patients went on to have an improvement in MDS-UPDRS Part 3 at 48 weeks. If these results are replicated, this observation may be useful in future trial design or to aid clinicians in deciding which patients may benefit from long term treatment thus reducing the cost and exposure to side effects associated with exenatide among patients experiencing insufficient clinical benefit.
Despite the limitations of any subgroup analysis, the effects of exenatide on motor severity in post hoc defined subgroups of patients are broadly consistent with the improvements in motor severity seen in the overall study population. The improvements in motor severity at 48 weeks were greater in the exenatide treatment group versus placebo in all subgroups, although unsurprisingly this did not reach statistical significance given the smaller sample sizes and the level of uncertainty (95% CI confidence intervals). However, treatment effects of exenatide on motor severity were broadly consistent with the mean improvement reported for the overall study, indicating that patients with a wide range of clinical features may potentially benefit. Regarding non-motor symptom outcomes and quality of life scores, there were significantly reduced responses to exenatide in patients with disease duration over 10 years and in whom symptom onset occurred after the age of 60 years. This may also be important for patient selection/stratification for future trials. Interestingly, there was an indication that patients with insulin resistance or obesity at baseline had better outcomes with regards to cognition. In patients with type 2 diabetes, previous studies have demonstrated that a greater beneficial clinical response to exenatide (lowering of HbA1c) can be predicted in patients with higher HbA1c values at baseline (Khan et al., 2015) and extensive links exist between insulin resistance, obesity and risk of cognitive impairment (Palacios et al., 2011; Talbot et al., 2012; De Felice et al., 2014; Kim & Feldman, 2015). In addition PD patients with concurrent Type 2 diabetes and insulin resistance have faster rates of cognitive decline compared to PD aged matched controls and this faster progression in the placebo group may explain why a possible effect of exenatide on cognition was detected (Giuntini et al., 2014). Again, this needs to be replicated. One proposed mechanism for any neuroprotective effects of exenatide involves the reversal of insulin resistance and restoration of insulin signalling pathways (Athauda & Foltynie, 2016) and it may be that that patients with dysfunctional insulin signalling incur a greater response, though this remains speculative.

In view of the width of the 95% CI confidence intervals, many of the suggested differential treatment effects may possibly be due to chance, and after conducting 26 independent statistical interaction
tests on each outcome measure (using a p value of 0.05), there is a high probability of finding at least one significant subgroup-by-interaction treatment effect (Lagakos, 2006), thus examining the general direction of effects and plausibility of any potential trends is important in generating future hypotheses. However, we did observe some consistency within these analyses, indicating that patients with an akinetic-rigid phenotype, and longer disease duration, exhibit a reduced motor response to exenatide compared to other subgroups. Previous studies have suggested patients with more severe disease and longer disease duration also exhibit altered responses to dopaminergic therapy (Hershey T et al., 2003; Kordower et al., 2013). Furthermore, older age of onset is known to be associated with a more severe motor phenotype and more severe dopaminergic dysfunction using Datscan imaging (Pagano et al., 2016). Older patients typically have a number of comorbidities compared to younger and this heterogeneity may also have implications for inclusion criteria and patient stratification for future putative neuroprotective/restorative therapies (Hershey T et al., 2003; Kordower et al., 2013). In conclusion, notwithstanding the limitations of such a post hoc analysis and providing the results can be replicated our data suggest that patients with more disease severity and longer disease duration may benefit less from exenatide than patients with less severity and shorter duration. These exploratory findings will contribute to the design of planned future trials that will need to confirm whether such heterogeneity of the effect of exenatide exists in a larger cohort of patients.

Further issues regarding optimal trial design also remain. Although assessing patients in the practically defined off medication state has been utilised in previous studies to assess underlying PD severity, assessments may be confounded by persisting long lasting effecting of levodopa. Conversely, evaluating potential disease modifying therapies in de novo untreated patients to remove this confound risks high dropout over time, especially in the placebo group and also increases the risk of inclusion of a biased cohort with milder disease progression. Maximising the signal of effect and reducing heterogeneity of response, can help mitigate the inevitable compromises associated with all PD disease modifying trial designs.
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Author contributions

TF (Principal Investigator) was responsible for study design, study oversight, statistical analysis, data interpretation and critical review and writing of the manuscript. DA, NB and LZ recruited and followed up the patients. TF, DA, SS, KC, SH were involved in the statistical analysis and data interpretation. DA, KM, IAO, PL, were responsible for study oversight and critical review of the manuscript. DA wrote the first draft, and all authors critically revised the report, commented on drafts of the manuscript, and approved the final report

Conflicts of interest

PL has received honoraria from Medtronic and St. Jude Medical. TF has received honoraria from Profile Pharma, BIAL, AbbVie, Genus, Medtronic, and St Jude Medical. All other authors declare no competing interests.
Figure legends

Table 1: Univariate and multivariate analysis of the association between baseline clinical features with change in MDS-UPDRS Part 3 at 48 weeks in patients treated with exenatide

Table 2: Baseline demographics and disease characteristics of responders / non responders in patients treated with exenatide

Table 3. Logistic regression model of prediction of response to exenatide (responder defined as change in MDS-UPDRS Part 3 > 3.25)

Figure 1: Subgroup analyses of Change in MDS-UPDRS at 48 weeks from baseline. P values are exploratory and do not represent statistical significance

Figure 2: Subgroup analyses of Change in total Non-motor symptom score at 48 weeks from baseline. P values are exploratory and do not represent statistical significance

Figure 3: Subgroup analyses of Change in total Parkinson’s disease Questionnaire-39 (PDQ-39) score at 48 weeks from baseline. P values are exploratory and do not represent statistical significance

Figure 4: Subgroup analyses of Change in Mattis-DRS2 score at 48 weeks from baseline. P values are exploratory and do not represent statistical significance
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