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The value of a Feasibility Study into long-term Macrolide therapy in Chronic Rhinosinusitis

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Preliminary data presented at the 2014 European Rhinology Society conference and the 2014 American Academy of Otolaryngology-Head and Neck Surgery meeting.

ABSTRACT

Objectives

There is currently conflicting level 1 evidence in the use of long-term antibiotics for chronic rhinosinusitis without nasal polyps. The primary aim of this feasibility study was to optimise future randomised trial design by assessing recruitment and retention of patients alongside providing preliminary data on symptomatic control.

Design

Prospective, multi-centre feasibility (cohort) study with all patients receiving macrolide therapy for 12-weeks and a further subsequent 12-week follow-up. Participants received a 12-week course of Clarithromycin 250mg alongside twice daily topical Mometasone and nasal douching. Primary outcomes focused on recruitment, retention and compliance. Clinical and quality-of-life outcomes measures were also recorded.

Setting

Patients were prospectively recruited from 6 UK outpatient clinics.

Participants

Adult patients with chronic rhinosinusitis without nasal polyps and no prior endoscopic sinus surgery underwent baseline assessment and then follow-up at 3 and 6 months.

Main outcome measures

Six-month recruitment and retention data.

Results

Over 13 months, 55 adults were recruited from 5 centres. Four patients declined participation. 75% of patients were retained within the study. Dropouts included 1 medication contraindication, 3 unable to tolerate medication, 10 not attending full follow-up. Sino Nasal Outcome Test-22 and endoscopic scores showed statistically significant improvement. No other clinical or quality-of -life assessment improvements were seen.

Conclusion

Retention and recruitment to a trial using long-term Clarithromycin to treat chronic rhinosinusitis without nasal polyps is achievable and this data will support a future Randomised Controlled Trial. The study provides vital insight into trial design thus informing UK research networks and rhinology researchers internationally.

Key Words: Macrolides, Sinusitis, Clarithromycin, Feasibility

INTRODUCTION

Long-term macrolide therapy is recommended in the treatment of Chronic Rhinosinusitis (CRS)[1]. Its potential benefits were extrapolated from findings in the respiratory community where marked improvement in both chest and nasal symptoms were seen in

panbronchioliitis patients alongside prolonged survival rates[2]. The anti-inflammatory effects of reducing cytokine activity and in turn reducing airway inflammation and mucus production are well documented[3]. In CRS there have only been two Randomised Control Trials (RCT) performed to date which show conflicting evidence; the efficacy of macrolides in treating the condition has been called into question due to this conflicting level 1 evidence[4,5].

The first double-blind RCT published showed a significant improvement in clinical scores (alongside other outcomes) with Roxithromycin in CRS without nasal polyps (CRSsNPs), particularly in the normal IgE subgroup[4]. A second RCT with a similar number of patients, using Azithromycin did not show a significant improvement between the macrolide and placebo group[5]. The Cochrane review into antibiotics for CRS concluded that Wallwork et al's study supported the therapy but further large sample studies were required[6]. This was echoed in a recent meta-analysis which found limited data to support macrolide therapy in CRS[7], stating further research is required. In addition it is recognised that the data from the most recent RCT[5] may skew outcomes as the study recruited predominantly patients who had failed previous sinus surgery, and included mixed phenotypes, with both CRSwNP and CRSsNP. Potentially more patients with elevated IgE levels who may not respond to macrolide therapy were recruited, although subgroup analysis was not performed[1]. With the increasing emergence of antibiotic resistance it is important that clinicians use such medications responsibly[8]. In addition clarithromycin use is associated with an increased risk of cardiac death particularly in women[9], hence evaluation of its use, especially in long-term therapy is essential.

A future RCT to clarify the use of macrolides in CRS must be sufficiently powered, use appropriate clinical assessment methods and ensure retention of patients leads to meaningful data collection. To inform this process we conducted a UK-based, multicenter feasibility study. The primary outcome measures were patient recruitment and retention to the study with secondary outcomes including assessment of medication tolerance and compliance to the study protocol. In addition feedback and clinical outcomes of the study are reported.

MATERIALS AND METHODS

Ethical Considerations

Ethical approval was given to the study from the West Midlands Research Ethics Committee (reference: 12/WM/0359) and the study was included on the UK CRN portfolio (ref: 13417).

Funding

Funding for the study was partly provided by the Royal College of Surgeons of England (Pump Priming Grant) with support from the Anthony Long and Bernice Bibby Trusts.

Methods

The study was conducted as a multi-centre collaboration between 6 sites. Study centres included James Paget University Hospital (Great Yarmouth), Guys & St Thomas Hospital (London), Royal Surrey County Hospital (Guildford), Queens Medical Centre (Nottingham), Freeman Hospital (Newcastle) and Queen Elizabeth Hospital (Birmingham). As this was a feasibility study, no sample size was needed but a target recruitment of 50 patients over a 12-month period was established at the beginning. At the

beginning of the study, the Chief Investigator hosted a teleconference with Principal Investigators and Research Nurses at all sites included.

Inclusion criteria

Inclusion criteria comprised of adult patients between 18 and 70 years, with a diagnosis of CRSsNPs as per the EPOS guidelines (Fokkens, 2012) who had not received maximal medical treatment previously. Previous surgery was not a reason for exclusion although no patients had undergone previous endoscopic sinus surgery, one patient had undergone previous maxillary balloon sinuplasty.

Exclusion criteria

CRSwNP and secondary CRS (eg Wegner's, immunodeficiency).

Treatment Regime

At all sites, patients received a 12-week course of Clarithromycin 250mg b.d. alongside b.d. nasal douching and intranasal mometasone, (2 squirts, each nostril b.d.), the latter two being continued for a further 12 weeks. Regarding the choice of macrolide used, Clarithromycin is a common macrolide used in the UK with broader microbial coverage than Erythromycin[10].

Participant Flow

Patients diagnosed with CRSsNPs were recruited from the outpatient clinics at participating sites and subsequently underwent 2 face-to-face study visits and a third interaction via postal correspondence (questionnaires and feedback only). Patients who completed the study were asked to comment on their participation in the trial (see appendix 1). Baseline clinical assessment included endoscopy (scored using the Lund-Kennedy endoscopic score[11], mucocilliary clearance testing (saccharin test), smell testing

(Sniffin' sticks), serum IgE levels, skin prick allergy testing and sinus CT with Lund-Mackay scoring [12]. All but the last 3 tests were repeated at visit 2 following the 12-week course of clarithromycin. The Sinonasal outcome test (SNOT-22 – a disease specific measure of HRQOL), SF-12 and EQ-5D questionnaires (both global measures of HRQOL[13, 14, 15].) were completed at all 3 encounters.

Statistical analysis

Statistical analysis of continuous variables was performed using paired t-tests and non-parametric tests used for non continuous data. In regards to SNOT22 scores, patients with a minimum clinical difference of 9 points on the SNOT-22 were considered to have had a clinical improvement in symptoms[16].

RESULTS

Primary outcome measures

Recruitment of patients

Over a 13 month period (January 2013-January 2014) 55 patients were recruited from 5 units, 51% were male and the mean age was 55 years (range from 21-81). Sixty-three patients were eligible but 8 declined. Despite ethical approval being confirmed in November 2012, it took until the following December for all 6 sites to finally complete research governance. At three sites, Research & Development offices chose to interpret the research protocol differently from the ethics committee resulting in a temporary suspension of the study for 2 weeks whilst the Medicines and Health Regulation Authority (MHRA) confirmed the study was not a Clinical Trial of an Investigational Medicinal Product (CTIMP). During the first 9 months of the study, only the lead site was open to recruitment leading to considerably different numbers of patient participating in each site (see table 1).

Retention of patients

At the recruitment stage, one patient was excluded during preliminary work-up as clarithromycin was found to be contraindicated although underwent all of visit 1 before this was identified. Three further patients were unable to take the full course of clarithromycin due to side effects and 10 patients dropped out (see table 1). Compliance with the study protocol fell towards the end of the study with 55 patients attending visit 1, 45 attending visit 2 and 41 completing visit 3. Recruitment and retention rates varied considerably between hospitals, seen in table 1.

Compliance with assessment and treatment

Adherence to the study protocol varied between sites with poor compliance of the research staff in performing some clinical tests (see table 2). The use of the Sniffin' Sticks was temporarily halted during the study due to confusion about their use (by the sponsor representative) and subsequently their status at MHRA, but this was later overturned and their use reinstated. The reasons for poor compliance to the protocol is varied, feedback from research nurses taking part can be seen in appendix 2. Logistical issues affected some sites e.g. difficulty getting hold of equipment (in particular Sniffin' sticks kit). In addition poor conduct of the compulsory elements of the protocol in 1 centre were noted.

Medication tolerance and compliance

Three patients suffered adverse effects during taking the medication (acid reflux, skin reaction, gastrointestinal symptoms) and a fourth had headaches for the first 2 weeks which resolved enabling full completion of the 12 week course.

Secondary Outcomes

Patient feedback

Twenty-six patients responded to the postal questionnaire: 18 patient patients reported no negative aspects, the same number of patients would be happy to take part in a placebo study. Three patients reported issues with the clinical testing (discomfort during mucocillary clearance and sniffin' stick testing). Constructive criticism regarding communication between the study centre and patients/GP, was also made. Patients also raised the question about the possibility of breaking the blinding process if there was no symptomatic improvement in a placebo-controlled trial.

Staff feedback

It came apparent during running the trial that experience of the research nurses (RN) involved in the trial was of differing levels from an experienced ENT trained RN (site 1), to experienced (but not ENT trained) RN (site 3), to inexperienced RN (site 6).. There were issues with implementation of the protocol, specifically using up-to date questionnaires and performing the compulsory tests. Unofficial feedback from clinicians also highlighted the fact that some RNs were unfamiliar with certain clinical tests (Sniffin' sticks) and the length of time this took to perform such aspects reflected negatively on patient recruitment (seen at site 6 where the RN actively discouraged patients from taking part due to the perceived time to perform the test).

Clinical Outcomes

Table 3 shows the clinical results from this feasibility study. Excluding the 4 patients unable to take their medication due contraindications/side effects, 45 and 41 patients completed all surveys at visits 2 and 3 respectively. Statistically significant reduction in

SNOT-22 scores were found at both 3 and 6 months. This was clinically significant (score reduction of 9 points or greater[16]) in 22/45 and 20/40 patients at 3 and 6 months respectively. Endoscopic scores also showed a statistically significant improvement. Positive mucopus culture were seen in 12 patients as baseline assessment.

No other statistically significant result was seen in other clinical outcomes of mucocillary clearance and smell testing. Serum IgE levels were recorded in 50 patients at visit 1, 43 patients had both IgE levels and 12-week SNOT-22 data (see table 4). A greater proportion of responders to therapy were seen in the patients with elevated IgE levels although this was not significant (69% vs 47%; p = 0.212) in contrast to the previous RCT[5].

Low levels of inhalant screen positivity were seen in allergy testing (performed in 51 patients overall, 50 of whom has RAST and 1 skin prick testing), 9 patients demonstrated inhalant screen positivity, 5 of such patients had elevated IgE also.

Lund-Mackay (LM) scoring of CT-paranasal sinuses was performed in 54 patients. There was no significant correlation between LM score and symptomatic improvement following treatment using the clinically significant SNOT-22 score (p = 0.636). At site 1 the number of patients progressing to surgery was 12 of the 35 patients (34%) completing the study (11 undergoing sinus surgery, 1 undergoing septoplasty).

Patient reported outcomes

EQ-5D analysis showed no statistical difference in either mean VAS score or any of the 5 health dimensions (seen in Figure 1a-1e) although patients reported higher rates of pain/discomfort and anxiety/depression.

SF-12 scores (both Mental and Physical Component) increased at both visits 2 and 3 from baseline. The improvements were modest and did not improve to that above the score expected for a 'typical adult'.

DISCUSSION

Synopsis of key findings

We aimed to investigate the feasibility of a 6-month trial where clarithromycin was given for 12-weeks showed a recruitment rate of 83% and a retention rate of 76%. There was an average recruitment rate of 4.23 per month across all sites in the latter part of the study. Compliance to the study protocol varied from site to site, specific issues regarding this are discussed below. The lead site recruited significantly more patients (recruitment rate of 3.17/month) with good retention rates of 92%, the results are somewhat skewed by the poor retention rates in some other centres. This initiates a discussion about factors that contributed to the variation seen and how these could be managed to improve overall study retention and data collection. Recognising these issues is vital in planning a future RCT.

Comment on recruitment, retention and study protocol

The results show a failure of comprehensive data collection at all sites. An incorrect version of one study questionnaire was uploaded onto the central study site at the start of recruitment which caused some understandable confusion. At one centre, the RN misinterpreted the requirement to perform other outcome measures from the protocol hence reducing clinical and questionnaire outcomes further. At another site, 8 patients identified by initial screening failed to consent after assessment with an inexperienced generic research nurse, and no patients at this site ever joined the study. Time to perform

outcome tests was cited as the greatest barrier to participation. It is notable that the RN at this site took over 45 minutes to perform olfactory testing, compared to 20 min by an experienced research nurse. Lastly the reduced number at some sites were in part due to significant delays in research governance approval meaning some centres were unable to recruit until the last 4 months. These difficulties were in stark contrast to the lead site which had an experienced research nurse with an ENT background who successfully recruited patients to the study throughout the 13 month duration with the loss of only 3 patients (2 due to drug side effects and 1 drop-out).

The experience of the research nurses at the individual sites had a big impact on their ability to both recruit patients and perform the relevant investigations, despite a teleconference at the beginning of the study to talk through the flowchart. This has demonstrated a clear need for a specific training day for all research nurses involved in any future trial. Research nurse support provided by UK local clinical research networks (LCRNs) is often generic in nature but will vary from site to site. Any future RCT would include a study training day to ensure all staff undergo standardised training and has also inspired a national ENT study day for all generic research nurses. Due to the limited funding for this study, a centralised database was not available, but this would be mandatory if a formal RCT is funded in due course, to allow for ease of secure data entry at site visits. This feasibility study has identified significant issues for reflection if a full scale RCT is to be conducted effectively. In addition 93% patients were able to take the full course of therapy without significant side effects with only 3 subjects unable to tolerate clarithromycin and with appropriate screening, no serious adverse events, despite concerns from recent publications[9]. There is a growing body of evidence (published after study design) that macrolide therapy in those with previous ischaemic heart disease or

prolonged QT-interval on ECG is associated with cardiac toxicity. While no patients in this feasibility study suffered such side effects, the cohort was small and hence any future RCT should exclude patients with such risk factors and include an ECG in pre-treatment investigations [17, 18].

Clinical results and comparison to other studies

It must be emphasized that this is not a placebo-controlled trial and that without a control arm the effect of intranasal corticosteroids and douching cannot be assessed. While the clinical results from this case cohort study suggests that a longer-term course of macrolide therapy may be therapeutically advantageous in up to 50% of patients with CRSsNPs, no firm conclusions regarding clinical effectiveness can be made without a control arm. However, the response rate seen in this feasibility study provides valuable information for trialists considering a formal RCT, as it can inform power calculations. In addition it is notable that no other clinical indicators (e.g. mucocillary clearance, smell testing) nor generic quality of life assessment showed any statistically significant improvement. The results support the need for a further RCT as suggested by a recent meta-analysis[7] which found limited data to support such therapy. In addition, within the wider medical community it is vital to ensure long-term macrolides are used responsibly in the face of increasing antimicrobial resistance.

This study was designed to capture potential issues prior to recruiting to a full RCT. Limitations in study design can be acted upon at this early stage, such as the limited data collected to assess patient compliance with medication. The study relied purely on patient self-reporting and in the future questionnaires/diaries could be used to clarify this further. As patients also raised concerns regarding the time taken to complete outcome

assessments, the number of outcome measures should be re-evaluated prior to a formal RCT to minimise participant burden and maximize recruitment. Encouragingly many patients reported positive experiences regarding study involvement and were happy to take part in a placebo-controlled trial.

CONCLUSION

This paper presents an honest account of the issues encountered when conducting a multi-centre clinical trial. The issues identified have been integral in informing study design for a future RCT into macrolide therapy. In addition, we are keen to share our experiences with other researchers in order to reduce research waste through poor recruitment and retention which can lead to both under-powered and/or unfinished trials. This is in keeping with advice in avoiding research waste as identified by Chalmers and Glasziou[19]. Clinical trials require extensive time and financial commitment. It is the responsibility of researchers to ensure patients who relinquish their time to participate in trials are recruited to well-designed, well-conducted studies; a feasibility study is an essential part of this process.

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AUTHORSHIP CONTRIBUTION

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Manuscript Preparation: J Bewick and C Philpott, all other authors edited and approved the manuscript.

REFERENCES

1. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinol Suppl. 2012; 23: 1-298.

2. Kudoh S, Azuma A, Yamamoto M, Izumi T, Ando M. Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin. Am J Respir Crit Care Med. 1998; 157:1829-32.

3. Tamaoki J, Kadota J, Takizawa H. Clinical implications of the immunomodulatory effects of macrolides. Am J Med. 2004; 117: 5S-11S.

4. Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. Laryngoscope. 2006; 116: 189-93.

5. Videler WJ, Badia L, Harvey RJ, Gane S, Georgalas C, van der Meulen FW, et al. Lack of efficacy of long-term, low-dose azithromycin in chronic rhinosinusitis: a randomized controlled trial. Allergy. 2011; 66: 1457-68.

6. Piromchai P, Thanaviratananich S, Laopaiboon M. Systemic antibiotics for chronic rhinosinusitis without nasal polyps in adults. *Cochrane Database Syst Rev*. 2011.

7. Pynnonen MA, Venkatraman G, Davis GE. Macrolide therapy for chronic rhinosinusitis: a meta-analysis. Otolaryngol Head Neck Surg. 2013; 148: 366-73.

8. Kessel AS, Sharland M. The new UK antimicrobial resistance strategy and action plan. BMJ. 2013; 346: f1601.

9. Svanstrom H, Pasternak B, Hviid A. Use of clarithromycin and roxithromycin and risk of cardiac death: cohort study. BMJ. 2014; 349: g4930.

10 Genoway KA, Philpott CM, Javer AR (2011). Pathogen yield and antimicrobial resistance patterns of chronic rhinosinusitis patients presenting to a tertiary rhinology centre. J Otolaryngol Head Neck Surg. 2011; 40: 232-237.

11. Lund VJ, Kennedy DW. Staging for rhinosinusitis. Otolaryngol Head Neck Surg. 1997; 117(3 Pt 2):S35-40.

12. Lund VJ, Mackay IS. Staging in rhinosinusitus. Rhinology. 1993; 31: 183-4.

13. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996; 34: 220-33.

14. Ware JE, Kosinski M, Keller SD. SF-12 : how to score the SF-12 physical and mental health summary scales. 2nd ed. ed. Boston, Mass: Health Institute, New England Medical Center; 1995.

15. Oemar M, Janssen B. EQ-5D-5L User Guide: EuroQol Group; 2013. Available at: http://www.euroqol.org/about-eq-5d/publications/user-guide.html. Accessed October 15, 2014.

16. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. Clin Otolaryngol. 2009; 34: 447-54.

17. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. N Engl J Med. 2012; 366: 1881-90.

18. Mosholder AD, Mathew J, Alexander JJ, Smith H, Nambiar S. Cardiovascular risks with azithromycin and other antibacterial drugs. N Engl J Med. 2013; 368:1665-8.

19. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. The Lancet, 2009; 374: 86-89.

Figure Legend

Figure 1a-e: The EQ-5D data is presented as percentage of patients reporting each level in each of the 5 dimensions at the 3 separate visits. Patients were self-caring, with good mobility (level 1) but had higher rates of problems with anxiety/depression and pain/discomfort. The 2 latter dimensions worsened in some patients at 6-month.

LEGEND: baseline – black; 3-months – dark grey; 6-months light grey.

Table 1 Centre No.	Visit 1 completion	Visit 2 completion	Visit 3 completion	Reason for dropout
1	38	36	35	2 – clarithromycin side effects; 1 DNA
2	7	1	1	6 DNA
3	6	4	3	1 – clarithromycin contraindicated; 2 DNA)
4	1	1	1	-
5	3	2	1	1 – clarithromycin side effects; 1 DNA
6	0	-	-	Patients deterred by RN

Table 1 shows the recruitment and retention rates at each of the 6 centres and summarises the reason for dropout, (DNA = did not attend).

Table 2	Visit 1 completion	Visit 2 completion	Visit 3 completion
SNOT-22 Q	54/55	45/51	41/51
SF-12 Q	53/55	44/51	41/51
EQ-5D Q	53/55	44/51	41/51
Endoscopic score	38/55	29/51	N/A
Saccharin Test	54/55	42/51	N/A
Smell Testing	49/55	36/51	N/A
IgE levels	50/55	N/A	N/A
Allergy testing	51/55	N/A	N/A
LM score	54/55	N/A	N/A

Table 2 shows the completion rates of each study component at the 3 study visits with total completion numbers shown before elimination for dropouts/intolerance etc taken into account. Only the first 3 components were required at visit 3. (Q = questionnaire). Allergy testing was either with skin prick tests or RAST.

Table 3.	Test Result (standard deviation)				
Clinical test (number of patients at Baseline/3 months/12months	Baseline	3 months	p-value	6 months	p-value
SNOT22 total score (54/45/41)	41.09 (21.765)	33.29 (23.96)	0.01	31.48 (24.36)	0.03
SNOT22 clinically significant*		22/45 patients (48.9%)	-	20/40 patients (50%)	-
Endoscopic score (38/29)	3.31 (1.26)	1.4 (1.56)	0.000		
Smell Testing (49/36)	24.05 (9.45)	23.69 (9.99)	0.983		
Saccharin Test (seconds) (54/42)	800.44 (376.72)	818.97 (531.25)	0.274		
IgE levels (ku/l) (50)	100.7 (114.48)		-		
Allergy testing Positive result	9/50 patients		-		
LM score (54)	8.65 (4.72)				
SF-12 Mental	46.82 (11.96)	47.05 (47.05)	0.705	49.33 (11.13)	0.617

Physical	47.7 (10.64)	48.91 (11.04)	0.279	47.63 (10.04)	0.515
EQ-5D VAS	75.59 (20.95)	76.64 (21.65)	0.967	75.7 (19.40)	0.648

Table 3 shows the raw data for each of the clinical components of the study. *Clinically significant improvement in SNOT22 score (>9 points)[16]. NS = not significant

Table 4	SNOT22 clinical improvement (≥9 points)	SNOT22 no clinical improvement
IgE elevated	9	4
IgE normal	14	16

Table 4 shows the proportions of IgE positive and negative patients with significant clinical improvement in SNOT22 scores.

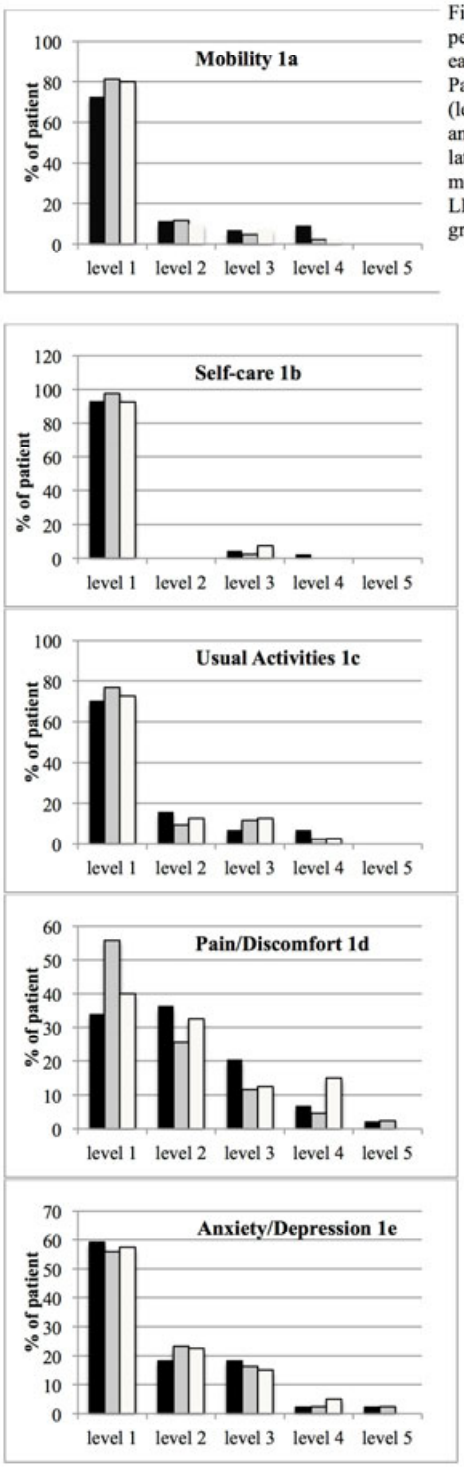

Figure 1a-e: The EQ-5D data is presented as percentage of patients reporting each level in each of the 5 dimensions at the 3 separate visits. Patients were self-caring, with good mobility (level 1) but had higher rates of problems with anxiety/depression and pain/discomfort. The 2 latter dimensions worsened in some patients at 6-month.
LEGEND: baseline – black; 3-months – dark grey; 6-months light grey.