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Original article

Medication adherence in older people with rheumatoid arthritis is lower according to electronic monitoring than according to pill count

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Abstract

Objectives. Suboptimal medication adherence is a serious problem in the treatment of chronic inflammatory diseases. To measure medication adherence, electronic monitoring is regarded as superior to pill count. GLORIA is an ongoing two-year trial on the addition of low-dose (5 mg/d) prednisolone or placebo to standard care in older people (65+ years) with RA. During the entire trial, adherence is measured with electronic caps, and with pill counts. The objective is to describe medication adherence patterns, and to compare the adherence results of the two methods.
Methods. The recorded adherence patterns of patients (blinded for treatment group) were classified according to descriptive categories. The cutoff for good adherence was set at 80% of prescribed pills taken.
Results. Trial inclusion closed in 2018 at 451 patients, but trial follow-up is ongoing; the current dataset contains adherence data of 371 patients. Mean number of recorded 90-day periods per patient was 4 (range 1–8). Based on pill count over all periods, 90% of the patients had good adherence; based on cap data, only 20%. Cap data classified 30% of patients as non-user (<20% of days an opening) and 40% as irregular user (different adherence patterns, in or between periods).
Conclusion. In our trial of older people with RA, the majority appeared to be adherent to medication according to pill count. Results from caps conflicted with those of pill counts, with patterns suggesting patients did not use the bottle for daily dispensing, despite specific advice to do so.
Trial registration. NCT02585258. ClinicalTrials.gov (https://www.clinicaltrials.gov/)

Key words: rheumatoid arthritis, glucocorticoids, medication adherence, electronic monitoring, pill count

CLINICAL SCIENCE

Rheumatology key messages

- Electronic monitoring as in our trial is not suitable to measure adherence in older people.
- Medication adherence as measured with caps was much lower than measured by pill count.
- The adherence pattern recognition and the developed descriptive categories may prove useful in other studies.

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Introduction

Suboptimal medication adherence is a serious problem in the treatment of chronic inflammatory diseases. Medication adherence, generally defined as the extent to which a person's behaviour (taking medication in our case) corresponds with agreed recommendations from a health care provider [1], is often below 50% in patients with chronic diseases such as rheumatoid arthritis (RA) [1, 2]. There are contradicting findings about the extent of adherence in older patients compared with younger patients [3]. Some studies in various diseases find better adherence with older age [4, 5] or no significant effect [6] and this conforms with findings in a recent review of studies in RA [7]. Other studies find lower adherence among older patients. As adherence (and suboptimal treatment) is adversely affected by multiple comorbidities and associated polypharmacy [6, 8–10], and the likelihood of this increases with age [11], the extent to which the study population is selected to be healthy may be an explanation for these conflicting findings. Poor medication adherence increases the risk of a flare of the disease [12] and subsequently likely leads to increased healthcare costs [13, 14].

Methods to measure medication adherence include questionnaires, pill counts, electronic monitoring and monitoring drug levels in blood or urine [15, 16]. However, there is no consensus about the best method. Monitoring drug levels is seen as the most reliable method if the half-life of the drug is appropriate [17], but it is costly and invasive, unless it can be combined with routine blood tests [17]. Electronic monitoring consists of a cap with an internal electronic device that records the date and time of each opening and closing of the bottle [15]. Such monitoring may be superior to pill count, which often overestimates the medication adherence [15]. Advantages of electronic monitoring include visibility of medication adherence patterns and changes in medication-taking behaviour [9]. Questionnaires often do not provide accurate and reliable assessments [15].

In the two-year Glucocorticoid Low-dose Outcome in RA (GLORIA) trial on the addition of daily low-dose (5 mg) prednisolone or placebo to standard of care in older people (65+ years) with RA, medication adherence was measured with electronic caps as well as pill count during the whole trial. The aim of the current study is to describe medication adherence patterns recorded by the electronic caps and to compare medication adherence as measured by electronic monitoring with that of pill counts.

Methods

The Glucocorticoid Low-dose Outcome in Rheumatoid Arthritis (GLORIA) study [18] is a two-year randomized, double-blind, pragmatic multi-centre trial on the addition of daily low-dose (5 mg) prednisolone or placebo to standard of care in older patients with RA. Patients diagnosed with RA (1987 [19] or 2010 [20] criteria), aged 65 years or older and with a disease activity score in 28 joints (DAS28) of $\geq$2.6 were recruited in one of the 28 participating rheumatology clinics in Germany, Hungary, Italy, The Netherlands, Portugal, Romania and Slovakia. Exclusion criteria were related to having lower probability of benefit, having higher probability of harm, difficulty in measuring benefit and/or harm, patients not capable or willing to provide informed consent (for details, see our protocol article [18]). For the adherence part of the study, no additional inclusion or exclusion criteria, such as the use of pill boxes or assistance with medication intake, were applicable because this is a pragmatic trial and we intended to exclude as few patients as possible.

Patients in the GLORIA trial received one or two new medication bottles with electronic caps (kits) at every clinic visit, for a total of at least eight bottles in 2 years. Some patients received one or more extra bottles of medication to cover extended periods between visits. Each bottle contained 90 capsules. Patients were randomized to receive daily 5 mg prednisolone or placebo. The treatment was double-blind, and the blind was kept intact for the current study because the trial is still ongoing. All patients gave written informed consent to participate in the GLORIA trial. Patients were instructed to open the medication bottle daily, preferably in the morning, and to take only the capsule for that day from the bottle. Patients were aware that their medication adherence was monitored by electronic caps and counting the returned pills. Patients also knew that the data of the caps were analysed anonymously after they finished the trial.

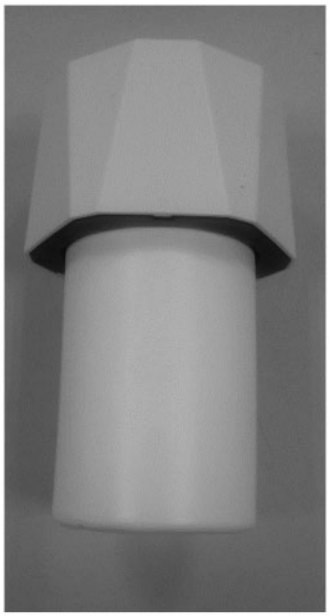
Assembling of medication kit

Both prednisolone 5 mg and matching placebo were manufactured by Bluepharma Indústria Farmacêutica, S.A., Coimbra. Study medication was primarily packaged in standard bottles (90 capsules) and, prior to release to clinical sites, individual labelling and manual assembling of the electronic cap was performed to yield the final medication kit (Fig. 1). All these activities were performed in accordance with cGMPs and EudraLex Vol 4, Annex 13: Investigational Medicinal Products. Electronic caps, named Smartcap, were developed and distributed by BeyonDevices LDA, Sobral de Monte Agraço, Portugal (see Supplementary Data 1 for system description of electronic cap, available at *Rheumatology* online). The functioning of the caps was internally tested.

Medication adherence measurements

Medication adherence was measured with two methods: electronic monitoring and pill (capsule) count. Any deviations in medication intake, such as no intake of medication because the patient forgot to take the medication bottle on holiday, were reported by the patient during the study visits at 3-monthly intervals. Caps were shipped back to the producer and read out in batches. For medication adherence according to electronic caps,

Fig. 1 Medication bottle used in the GLORIA trial



the assumption was made that a bottle opening was equal to the intake of one capsule [21, 22]. Intake according to electronic caps was calculated by subtracting the number of days that the cap was not opened from the total days between visits. Two technical problems with the cap reports received from this product had to be resolved in the analysis phase. First, time records included min, h and date as day-month but not year, creating problems with periods crossing the year change; and days without opening did not generate any record, resulting in 'skipped' dates.

Medication adherence according to pill count was calculated as follows: if the number of capsules dispensed is D, the treatment period in number of days is P, and the number of capsules returned is R, medication adherence (expressed as %) is calculated as: 100*(D−R)/P.

In alignment with the literature [23], good medication adherence was defined as an intake of at least 80% of the prescribed doses. The proportions of patients with good medication adherence according to electronic monitoring and pill count were compared. The implementation of the medication was represented by the proportion of days with the correct number of doses taken (i.e. one opening per day).

Medication adherence patterns

The medication adherence patterns of the patients were categorized according to the opening pattern seen in at least 50% of the assessed periods. The following descriptive categories were defined:

i. Non-users: <20% of the days one opening;
ii. Stable users: ≥80% of the days one opening;
iii. Weekly users: one opening per week;
iv. Irregular users: different or unclassifiable medication adherence patterns, in or between periods.

Insights about the use of the electronic caps

From each medication adherence pattern, one to three patients with the most convincing pattern in their category and who finished the trial in the past few weeks were selected for a semi-structured telephone interview. The interviews were guided with a set of four questions, but additional questions were allowed to obtain all relevant information. The purpose of the interview was to gain insight into how patients used their cap; for example, if they opened the bottle only once a week because they used a weekly pill box. As GLORIA is a pragmatic trial, all patients were included in electronic monitoring; patients with a weekly medication dispenser were advised to use the GLORIA medication bottle for the study medication.

Post-hoc analyses on cap medication adherence

An exploratory analysis searched for baseline factors correlated with cap medication adherence. First, the number of comorbidities, number of co-medications, age, sex, duration of RA, morning stiffness severity, disease activity (DAS28), HAQ, amount of pain, physician global assessment of disease activity, evidence of structural joint damage and education level were included as univariate factors in a linear regression with cap medication adherence as the dependent variable. Then, variables correlated with $P \leq 0.10$ were included in a backward linear regression model.

Results

The trial inclusion has closed in 2018 at 451 patients. The current dataset contains adherence data of 371 patients for the electronic caps and 416 patients for pill count (Fig. 2): 70% female, mean age 73 (s.d. 5, min–max 65–87) (Table 1). The number of patients for electronic caps and pill count data differed because not (yet) all caps were returned for the data extraction. Thirty-two patients were excluded from the dataset because they didn't have any medication adherence data or because they discontinued the trial during the first period. Included patients have a minimum of one and a maximum of five electronic cap measurements and/or a minimum of one and a maximum of five pill count measurements. For pill count, 38 measurements of 35 different patients were excluded because they were an inexplicable outlier (range: 110–184%; further information in Supplementary Data 2, available at *Rheumatology* online). A total of 9% of returned caps did not contain data and an additional 7% contained little data (between 0 and 5% of expected openings).

The mean number of recorded 90-day periods per patient was four (range 1–8). The median medication adherence per single period was 99% (inner quartile interval, Q1–3: 94–100) according to pill count and 46%

Fig. 2 Flow chart of patients included in the adherence analyses

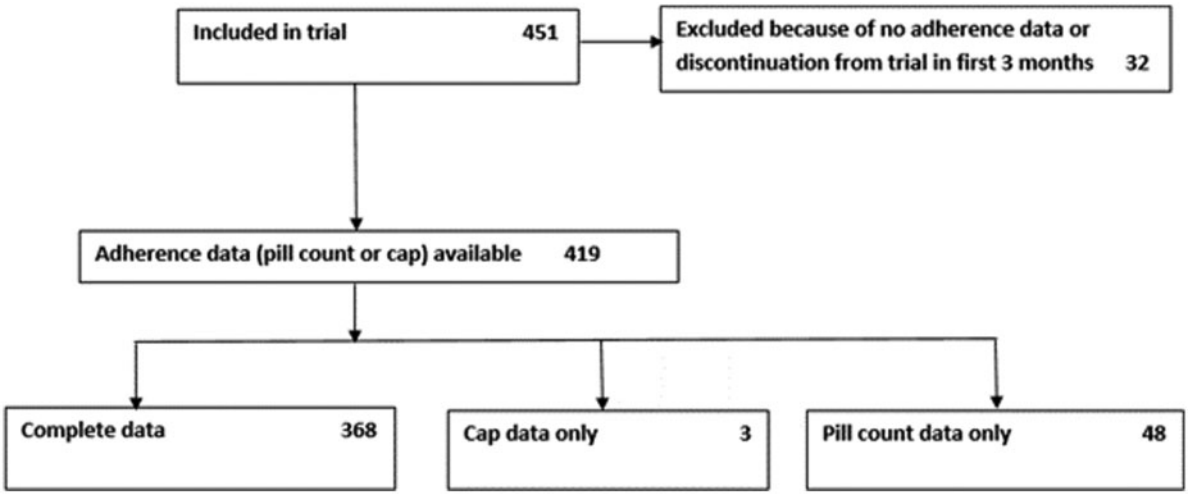


Table 1 Demographic characteristics and disease activity measurements at baseline

Characteristic at baseline	Patients included in the analyses (n = 419)
Female, *n* (%)	291 (70)
Age, years	73 (5)
Educational level:	
Primary school, *n* (%)	124 (30)
Secondary school, *n* (%)	213 (52)
Higher education, *n* (%)	76 (18)
RF, *n* (%)	274 (65)
Anti-CCP positive, *n* (%)	236 (56)
Evidence of structural joint damage, *n* (%)	177 (42)
RA duration, years	10 (10)
Number of comorbidities	3.7 (3.2)
Number of concomitant medications	7.4 (3.6)
DAS28	4.8 (1.9)
Pain (scale 0–10)	5.4 (2.4)
HAQ (scale 0–3)	1.2 (0.7)
Morning stiffness severity (scale 0–10)	5.0 (2.4)
Physician global assessment of disease activity (scale 0–10)	4.6 (2.0)

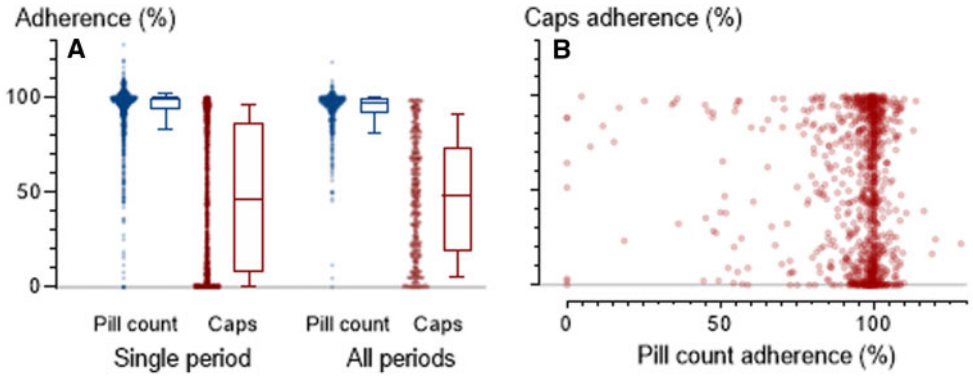
Data are expressed as mean (S.D.), unless otherwise reported.

(Q1–3: 8–87) according to the caps (Fig. 3A). Over all periods, the median medication adherence was 97% (Q1–3: 92–100) measured with pill count and 48% (Q1–3: 19–74) measured with electronic caps (Fig. 3A). Based on pill count over all periods, 90% of the patients had good medication adherence as defined in the methods; according to the caps only 20% met this criterion. The scatterplot shows that medication adherence according to pill count did not correlate with medication adherence according to electronic monitoring (Fig. 3B). According to electronic monitoring, most patients did not implement the medication as required; the average proportion of days on which the correct dose was taken is 44%.

The medication bottle was specifically designed with a large cap, mindful of the need of patients with impaired hand function (Fig. 1). Nevertheless, in the beginning of the trial several centres reported that patients had problems with opening and closing the bottle. The design of the electronic cap was subsequently slightly altered, but the problem was still reported. Also, recorded medication adherence patterns were not noticeably different before and after the design improvement.

The medication adherence patterns of the bottles with an electronic cap illustrate bottle use (Fig. 4). Most patients showed irregularity within and between periods. For example, in one period the cap was not opened

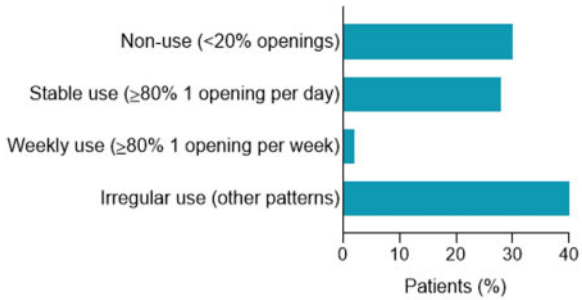
Fig. 3 Medication adherence measured with pill count and electronic caps



(A) Medication adherence measured with pill count (blue) and electronic caps (red) per single period and over all periods. Individual results left, boxplots (whiskers indicate p10 and p90) on the right. **(B)** Scatterplot of medication adherence (%) per single period according to pill count *vs* electronic caps.

Fig. 4 Examples of medication adherence patterns Yellow: no opening; green: 1 opening; blue: ≥2 openings on that day.

Fig. 5 Patients categorized by their predominant pattern of electronic cap use



(non-use pattern in Fig. 4), while in another period the cap was opened more frequently but still not every day (irregular use pattern in Fig. 4).

Over all periods, for electronic monitoring most patients were classified as non- or irregular user: 30 and 40%, respectively (Fig. 5). Only a quarter of the patients (28%) used the bottle with electronic cap as prescribed, i.e. one opening per day on ≥80% of the days. A few patients (2%) used a weekly pill box, which was seen in the medication adherence patterns. Some patients (2%) had periods of over-use, i.e. opening the bottle more than one time per day, but this pattern was not consistent over multiple periods. No trend was seen over time, e.g. decreased use of caps after initial regular use, either within or between periods. For pill count, there was also no trend over time seen for decreased or increased adherence between periods.

Interviews

Ten patients, one to three of each of the five medication adherence patterns, were interviewed about how they used the medication bottle with electronic cap, and the impression of the research nurse was also noted. Four patients reported that they had difficulties closing the bottle and two patients indicated that they took all of the required number of pills from the bottle if they went on holiday.

In six patients, the recorded patterns correspond with the bottle use according to the patient. Two patients opened the bottle daily, as was also seen in their medication adherence patterns. One patient indicated that the bottle was not opened, except for a first opening by the pharmacy, because it was difficult to close the bottle; thereafter, the patient took the medication daily, from the open bottle. Correspondingly, the medication adherence pattern showed non-use because the cap was never closed. Two patients confirmed their irregular medication adherence patterns due to forgetfulness and the use of a weekly pill box which was irregularly refilled. The final patient confirmed her weekly use as recorded.

In the remaining four patients, the recorded pattern did not (fully) correspond with the use reported by the patient. Two patients had a few periods of over-use, but both patients reported opening the bottle always once per day. One patient had a non-use pattern and the nurse confirmed this, but the patient still reported

opening the bottle every day. Another patient reported opening the bottle every day and the nurse confirmed this presumption. However, the medication adherence pattern showed irregular use of the bottle.

Correlations with medication adherence

Higher cap medication adherence was univariately weakly associated with male sex, younger age, lower number of co-medications, and less disability (HAQ); correlations between 0.11 and 0.15. The first three factors were retained in the multivariable model with an overall explained variance (R^2) of 0.22.

Discussion

This study suggests that electronic monitoring as implemented in our trial is less suitable than pill count to measure medication adherence in older people with RA. Most patients did not implement the dosing regimen, i.e. they did not open (or close) the bottle daily as prescribed, but irregularly or rarely instead. Interviews suggested this was at least in part due to difficulties with opening the bottle or use of other pill boxes that were intermittently filled from the study medication bottle. Subsequently, medication adherence as measured with electronic caps (48%) was much lower than that measured by counting the returned capsules (97%). The medication adherence measured with electronic caps and pill counts remained respectively low and high over time, suggesting that patients are consistent in their medication use and the use of the cap. Despite the failure of the electronic caps in our study, we implemented a novel method of pattern recognition and defined descriptive categories that may prove useful in other studies.

To our knowledge, this is one of the largest and longest studies among older RA patients on electronic monitoring to measure medication adherence in the context of a clinical trial. Most previous studies describe shorter periods of monitoring in routine care. The results of these studies are heterogeneous. Some document non-adherence to medication and irregular openings as in our study [21, 24, 25]; others show concordance between pill counts and electronic monitoring [26, 27]. The remainder fall in between, with medication adherence between 59% and 92% [22, 26, 28–31].

True problems with medication adherence will obviously cause a record of non- or inconsistent adherence, or rarely, of over-adherence, and the expectation is that this will be better detected by electronic caps than by pill count. Patients can (inadvertently or purposefully) manipulate cap data by opening the bottle without taking the medication or pill count by removing part or all of the remaining pills [22, 28]. However, a scoping review reported a median difference of about 8% between electronic cap and pill count medication adherence [15].

In our study, the large difference in adherence between electronic caps and pill count could theoretically be declared by social desirability. In that scenario, non-adherent patients could have removed pills from the bottle because they were aware that the returned pills would be counted in the clinic. The electronic caps also monitored adherence, but maybe some of the patients forgot this or they were less concerned about this because the data were read out at a company at a later time point. The interviews did not support such a scenario, but here the patients could have given socially desirable answers.

In the above scenario, the low medication adherence measured with electronic monitoring in our study could be the true value, but we feel the large discrepancy is better explained by other reasons. It is more likely that a substantial number of patients in our study did not open or close the bottle every day as instructed, even though they took a capsule every day. Reasons for this included difficulty with opening and closing the electronic cap, but also alternative pill boxes, vacation etc.; this was confirmed in the interviews. Problems such as these are more likely in older people on multiple drugs, and in patients with functional limitations, especially in the hand. Data about hand function are not available for this study; overall physical disability was weakly correlated with worse cap medication adherence, but morning stiffness was not. Unfortunately, our electronic cap form frequently caused difficulties despite its design, but the impact of this design flaw could not be fully assessed or addressed because readout was performed with a long lag time, discontinuously and off-site in batches. Also, incorrect cap activation or malfunction may have occurred [32]. Multiple openings on a day could be out of curiosity [22] or to check the number of remaining pills [33].

Trials in older people pose significant challenges in recruitment and retention [34]. In retrospect, substantial piloting of the product and its accompanying software, close monitoring of problems and patient feedback in the initial phase of the trial might have resulted in a better outcome for this type of electronic monitoring.

This study suggests that electronic monitoring as implemented here is not suitable to measure long-term medication adherence in older people with RA in the clinical practice or clinical trials where patients take concomitant medications. For such patients, pill count is more suitable, or monitoring of blood levels where feasible.

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The study complies with the Declaration of Helsinki. The ethics committee of Amsterdam UMC, location VUmc has approved the research protocol. Informed consent has been obtained from the subjects.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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