Medication adherence reporting in pivotal clinical trials: overview of oral oncological drugs

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ABSTRACT

Objectives To assess how and to what extent adherence to medication is reported in pivotal clinical trials of oral cancer drugs.

Methods All drugs authorised by the European Medicines Agency from 1 January 2014 to 31 December 2019 were considered for analysis. For each pivotal trial we extracted the journal of publication, phase of the study, posology, mention of adherence within the main text of the published article or additional material and the terms in which the adherence was reported.

Results Thirty drugs were included in the analysis from 56 clinical trials. Eleven articles (19.6%) contained a mention of medication adherence in the main document, 26 (46.4%) in the supplementary material and 19 (33.9%) did not contain any reference to adherence. Seven studies reported medication adherence between the results, expressed as number of patients discontinuing treatment for non-compliance and mean or median percentage.

Conclusions Medication adherence in pivotal clinical trials of oral oncological drugs is poorly represented. There should be a greater level of reporting in the results and it should be included among the minimum set of recommendations in reporting health research.

INTRODUCTION

Medication adherence is the extent to which patients take medications as prescribed by their healthcare providers.[1] It is an essential factor in clinical practice, where it has a crucial role in determining clinical and economic outcomes in various therapeutic areas.[2–4] Many studies evaluate the medication adherence rate using direct and indirect methods,[5] which often result in low rates[6 7] due to many factors that can influence adherence.[8] As a consequence, it is important to measure and improve medication adherence in clinical practice.[9] This is true for various therapeutic areas including the treatment of cancer,[10–12] which is increasingly being treated as a chronic disease.[13] For example, it has been shown that, in kidney cancer, suboptimal adherence to treatment leads to lower drug exposure and consequently to lower progression-free survival, and in breast cancer it was found that adherence to treatment of less than 80% was associated with a reduction in survival.[12 14] Such low rates of adherence are due to multiple factors related to the patients, their socioeconomic conditions, the treatment and the condition.[15]

Numerous methods of measuring medication adherence have been proposed and studied, including direct methods based on measuring the amount of the drug taken by measuring the amount of drug or a metabolite in the patient's blood or urine and indirect methods which assess adherence from the data collected in patient questionnaires or from pharmacy and hospital dispensing data.[16] A questionnaire routinely used to assess adherence is the Morisky Medication Adherence Scale (MMAS),[17] while indirect methods of calculation from dispensing data include the Medication Possession Ratio (MPR)[18] or the Proportion of Days Covered (PDC),[19] which calculate the number of doses taken by the patient in relation to the number prescribed. Pill counting consists of physically counting the pills that have not been taken and are therefore still in the possession of the patient at each dispensing cycle.[20] The Medication Event Monitoring System (MEMS), on the other hand, is a more advanced and costly calculation system which uses special drug packages that record the number of times the patient takes a tablet.[21]

In clinical trials, intensive resources are dedicated to maximising medication adherence where adherence levels need to be high.[22] However, certain factors may lead to non-optimal rates causing an increase in the variance of the sample, a weakening of the power of the study and a reduction in the potency of the effects of the treatment,[23 24] resulting in negative regulatory and public health consequences.[25]

In 2003 Cramer *et al* and in 2012 Blaschke *et al* respectively showed that adherence in clinical trials can have suboptimal values and that non-adherence is not an isolated phenomenon. This has repercussions on the internal validity of trials and the resulting levels of efficiency and safety, thereby making it necessary to take steps to measure and monitor therapeutic adherence.[26 27]

Accurate reporting of data in properly designed randomised clinical trials improves the correct interpretation of scientific medical papers,[28] but the medication adherence rate is often under-reported,[29] even in the field of oncology.[30] Among the proposals for improving reporting in clinical trials, there are those also related to adherence to treatment which can help to inform the statistical analysis, trial interpretation and choice of appropriate adherence strategies to implement in future trials and clinical practice.[31] In 2018 De Geest *et al* proposed a guideline to standardise the management and reporting of therapeutic adherence in clinical trials.[32]

The aim of this study is to evaluate how and to what extent the medication adherence rate is being reported in pivotal clinical trials of oral cancer drugs

for solid tumours which have been approved on the market since 2014.

METHODS

All the pivotal trials of oral cancer drugs for human use approved by the European Medicines Agency (EMA) between 1 January 2014 and 31 December 2019 were considered in the analysis. All commercialised drugs were downloaded from the EMA website's 'Download section'. Only orally administered drugs intended for human patients with solid tumours with Anatomical Therapeutic Classification (ATC) L01 approved between 1 January 2014 and 31 December 2019 were included. Therefore, from the list taken from the EMA website we excluded all veterinary drugs, drugs not approved for commercial use, drugs with an approval date before 1 January 2014, drugs with an ATC other than L01, drugs with haematological indications and those requiring parenteral administration.

For each of these drugs, one of the authors of this paper (RL) extracted pivotal clinical trials from section 5.1 of the Summary of Product Characteristics. RL and FS operating independently extracted the following data from the published papers on each of the pivotal trials:

▶ Drug: active ingredient
▶ Trial phase: I, II or III
▶ Study design: open-label or double-blind
▶ Posology of the experimental treatment
▶ Any mention of medication adherence: full text and study protocol, if any, have been read in full
▶ Journal in which the pivotal study was published

In cases where the extracted data by the two authors were different, a third author (AR) was involved to summarise and present the data.

For the analysis, we reported the percentage of studies that cited medication adherence in the main document or in the supplementary material and protocol, dividing them up according to the trial phase, journal of publication, type of cancer, study design and type of treatment in the control arm.

RESULTS

The results are shown in table 1 and in the online supplemental materials section.

We considered 56 pivotal clinical trials for 30 drugs, four phase I trials, one phase I/II trial, 15 phase II trials and 36 phase III trials. The treatment posologies were very diverse, ranging from 1 tablet once a day to 3 tablets twice a day of vemurafenib + 3–5 tablets of cobimetinib with dosage regimens which required 21 days of treatment followed by 7 days without.

Eleven studies (19.6%) reported medication adherence in the main document, two of which specifically used the term 'medication adherence' and nine used the term 'compliance'. Three of these 11 studies cited adherence/compliance in the Methods section, seven in the Results section and one in a section entitled Implications of all available evidence.

Adherence reported in the Results section

Seven of the 56 pivotal clinical trials (12.5%) gave information on medication adherence of patients under treatment. Five studies (71%) reported only the number of patients who were non-compliant (1–18 patients),[33–37] one trial (15%) reported the mean rate of adherence of 85%[38] and one trial reported both the number of patients who discontinued (n=2) and the median rate of adherence of 90%.[39]

Table 1 Reporting of medication adherence in pivotal clinical trials

	Studies (N)	Adherence in article N (%)	Adherence in supplementary material N (%)	No
Total	**56**	**11 (20%)**	**26 (46%)**	**19 (34%)**
Cancer type				
Basal cell	1	1 (100%)	0	0
Breast	8	1 (12.5%)	5 (62.5%)	2 (25%)
Colorectal	1	0	1 (100%)	0
Hepatocellular	2	0	1 (50%)	1 (50%)
Lung	21	3 (14%)	9 (43%)	9 (43%)
Melanoma	10	2 (20%)	4 (40%)	6 (60%)
Ovarian	5	3 (60%)	1 (20%)	1 (20%)
Prostate	2	0	2 (100%)	0
Renal	4	1 (25%)	2 (50%)	1 (25%)
Thyroid	2	0	1 (50%)	1 (50%)
Study design				
Double-blind	22	7 (32%)	10 (45%)	5 (23%)
Open label	31	4 (13%)	16 (52%)	11 (35%)
Control arm				
Comparator	18	2 (11%)	12 (67%)	4 (22%)
Placebo	11	4 (31%)	5 (45%)	2 (19%)
Placebo+drug	10	2 (20%)	5 (50%)	3 (30%)
Phase				
I	4	0	0	4 (100%)
I/II	1	0	0	1 (100%)
II	15	4 (27%)	5 (33%)	6 (40%)
III	36	7 (20%)	21 (58%)	8 (22%)

Adherence reported in the Materials and Methods section

One trial cited 'compliance' in the Methods section among the patient conditions that could interfere with compliance to be included in the exclusion criteria, one trial reported that compliance was monitored throughout the trial and one trial reported that non-compliance represented a cause of discontinuation. None of the studies that cited 'compliance' in the Methods section cited 'compliance' in the Results. One trial reported that the reduced pill burden might contribute to improved patient compliance in the Implications of all available evidence section, but referred to a different formulation of the same drug and not to the result of the trial.

Reported adherence in the supplementary material

In 26 of the 56 studies (46.4%), information on compliance was reported in a specific section within the supplementary materials. Seventeen of 21 protocols (80.9%) reported how compliance was assessed in the trial, with the vast majority of them (15/17, 88%) using a pill count approach. In one trial patients were instructed to notify a member of staff at the study site of any missed doses. In another the evaluation was carried out by means of a therapy diary delivered to the patient. In two protocols it was specified that the patient should take ≥75% of the planned doses to be deemed compliant, while in two other protocols it was reported that, to be considered compliant, each study patient must have received at least 80% of the planned number of doses. In one protocol it was reported that if the dosage compliance was not 100%, then investigators or designated staff members on the study site should re-instruct subjects regarding proper dosing procedures for the subject to continue in the treatment study. In two protocols it was specified that if compliance fell below 85%, a check-in call from a site staff member was recommended to ask

the subject if he/she had any difficulties. Two protocols reported the psychological, familial and social conditions of patients that could interfere with compliance to be included in the exclusion criteria. Finally, two protocols contained the definition of compliance within the protocol.[40 41]

Adherence not reported at all

Nineteen of the 56 studies (33.9%) made no reference to medication adherence in either the main document or in any of the additional material. None of the phase I and I/II trials reported any adherence data in either the main document or in the additional material. Of the 15 phase II trials, six (40%) did not report medication adherence, five (33%) cited medication adherence in the additional material and the remaining four in the main document, three of which were in the study results. Of the 36 phase III trials, seven did not mention medication adherence, 22 mentioned it in the additional material, seven in the article, of which four were in the study results. The only phase III trial with the non-inferiority design did not make any reference to therapeutic adherence.

Reported adherence by journal of publication

The trials considered have been published in four different journals and grouped according to journal: 25 in *Lancet Oncology* (of which seven reported medication adherence in the main document), 21 in the *New England Journal of Medicine* (of which two reported medication adherence in the main document), 9 in the *Journal of Clinical Oncology* (of which two cited medication adherence in the main document) and one in the *Journal of Thoracic Oncology*.

Reported adherence by type of cancer

When grouped by type of cancer, the pivotal trials relating to drugs for the treatment of ovarian cancer more often cited adherence in the published article (3/5), while in trials relating to breast and lung cancer the adherence data were under-reported in the articles (1/8 and 3/21 reported adherence in the article, respectively).

Reported adherence by study design

With regard to the different study designs, double-blind randomised clinical trials reported adherence data in the article more often than open-label trials (32% vs 13%).

DISCUSSION

The findings are in line with previous reports,[30] suggesting that this is not the direction in which things are moving.

As shown in the results and in table 1, adherence is very poorly reported in pivotal trials regardless of the type of drug, prescription and dosage.

To refer to medication adherence, the term 'compliance' is used more often in clinical trials than the term 'adherence', probably because medication adherence is the "degree to which the person's behaviour corresponds with the agreed recommendations" whereas 'compliance' implies patient obedience to the physician's authority.[42]

Clinical trials aim to evaluate the efficacy and safety of a new treatment rather than treating a single patient and, in the trial, adherence to the protocol must be guaranteed. In fact, in some protocols it is specified that, where conditions exist that hinder good compliance, the patient is excluded a priori from the trial[43 44] or that non-compliance may lead to discontinuations.[33–37]

In two protocols adherence has been defined as (1) compliance (%) = (total cumulative actual dose/(duration of study treatment * full dose prescribed per day))*100 and (2) as the number of capsules taken divided by the expected number of capsules and reported as a percentage. In the first case, rather than adherence to the treatment, this definition corresponds to the relative dose intensity, which takes into account dosage adjustments compared with the full dose.[45]

The adherence cut-offs within which patients meet the adherence requirements as defined by each trial, when reported, are not always the same. In fact, in some studies the value is established at 75%[46 47] but in others at 80%.[48 49] Thus, a varied framework of reporting, definitions and measurements of adherence emerges, which is probably based more on arbitrary estimates of the authors of the clinical trial than on evidence-based data.

The fact that the only two trials that report the definition of adherence report different definitions and that, of the four trials that report adherence cut-offs, two report a value of 80% and two 75% makes it clear that there is little clarity in the assessment of therapeutic adherence in the discrimination between adherent and non-adherent patients. Consequently, the assumption that in clinical trials therapeutic adherence is always optimal is based more on a conviction than on a measurement-based conclusion.

Most of the articles that report the methods to measure medication adherence use the pill count, which is a good method of calculation in clinical practice as it is practical and economical. However, for clinical trials, other more reliable methods such as MEMS could be used.[21 50]

The posology indicates that in many cases the dosage regimen is complex, with a high number of tablets in multiple daily administrations[51] and different routes of administration.[49] Complex dosage regimens can heavily influence therapeutic adherence in clinical practice[52] and this suggests, as with clinical trials, that patients with complex dosage regimens may find it more difficult to adhere to treatment, thereby highlighting the need for increased monitoring and reporting.

In comparative trials it is important that the adherence is superimposable in the control arm and in the experimental arm because, in the case of different adherence rates, the efficacy of the treatment could be under- or over-estimated. If the adherence rate is significantly higher in the experimental group, the efficacy of the experimental treatment could be overestimated while, likewise, if the rate of adherence is significantly higher in the control group, the efficacy of the experimental treatment could be underestimated. In the case of comparison with a placebo, the risk of suboptimal adherence would underestimate the efficacy of the experimental treatment.[53]

When a protocol is available in addition to the main document, a section is almost always dedicated to therapeutic adherence,[33 41 43 44 46–49 51 54–71] indicating that at the time of conception and definition of the study, and during the study itself, attention to the monitoring and to the optimisation of adherence is high. What is certainly lacking is documented evidence of such attention in the actual reporting.

The fact that adherence has not been reported is not necessarily an indication that adherence was not assessed, measured or implemented. However, it means that if it was done, it has not been reported, so the reader has no way of knowing if adherence was considered or not.

With regard to the journals, few of them reported adherence in the Results. Only three of 25 studies published in *Lancet Oncology*, two of 21 published in the *New England Journal of Medicine* and two of nine published in the *Journal of Clinical Oncology* cited adherence.

At present, proposals have been made both to standardise the evaluation of adherence in clinical trials and to include medication adherence among the standards with which to evaluate the quality of clinical trial reporting.[72]

Incomplete or inconsistent reporting in clinical trials has a negative impact on patient care and in general on research, because to understand and interpret the results of a study it is necessary that the data are reported thoroughly and consistently and with complete transparency.[73] When the issue of the importance of complete reporting was raised, the scientific community became increasingly more sensitive to the issue and, as a result, standards and practices have improved over time.[74]

With regard to adherence to treatment, we have shown that we are very far from having optimal levels of reporting, and considering that this is such an important factor,[25] this study indicates there is a need for greater caution. The adherence reporting in clinical trials is very important because the consequences of a lack of adherence in a clinical trial can be serious: they can lead to therapeutic failure and, if adherence is suboptimal, patients will have less efficacy than expected, which may lead to higher doses being considered effective than those included in the drug's label, putting patients at greater risk of adverse events.[25] It is therefore necessary to assess adherence objectively and not just by asking patients to self-assess.

Government agencies and bodies such as the EMA and the Food and Drug Administration (FDA) are also sensitive to the reporting of medication adherence in clinical trials. The EMA recommendations call for consideration of the importance of accurately defining and recording non-adherence events and their cause (eg, toxicity).[75] The FDA suggests identifying and selecting the most likely adherent patients prior to randomisation in order to minimise variability in drug exposure.[76]

CONCLUSION

Optimal rates of medication adherence are fundamental to the success of a clinical trial in the same way as randomisation. Non-optimal rates in one of the two arms is enough to cause an underestimation or overestimation of the results. Despite this, medication adherence is generally given little value, especially in the presentation of clinical trial results. Instead, it would be appropriate to indicate adherence rates in the results. This could be useful on two different levels: (1) to assess whether the efficacy and safety expressed in clinical trials can be influenced by adherence rates and (2) to give indications on the patient adherence rate that clinicians should expect in clinical practice.

What this paper adds

What is already known on this subject
⇒ Medication adherence is a key factor in a good response to treatment
⇒ Medication adherence in clinical trials is not necessarily good
⇒ Medication adherence is critically under-reported in clinical trials

What this study adds
⇒ This study highlights the lack of information about medication adherence and the need for it to be represented in clinical trials.

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