

BMJ Open Medication adherence among allogeneic haematopoietic stem cell transplant recipients: a systematic review protocol

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ABSTRACT

Introduction Patients receiving a haematopoietic stem cell transplant (HSCT) are subjected to complex oral medications based on prophylactic and immunosuppressive treatments. Adherence to medication plays a role in survival, and medication non-adherence (MNA) is closely associated with graft-versus-host disease and other complications. The aim of this systematic review is to summarise the available evidence regarding prevalence rates of medication adherence, the risk factors of MNA, the effectiveness of interventions to increase medication adherence and the outcomes associated with MNA.

Methods and analysis We designed a systematic review according to the Joanna Briggs Institute methodology. We will search the Cochrane Library and the CINAHL, EMBASE, MEDLINE via PubMed, PsycINFO and Scopus databases. We will include published and unpublished primary studies: (a) on humans, from inception until 10 May 2022; (b) written in any language; (c) experimental (randomised and non-randomised), observational (prospective, retrospective cohort and case-control), correlational, cross-sectional and longitudinal; and (d) with a low risk of bias, according to the quality assessment we perform. We will exclude secondary and qualitative studies, protocols, publications without original data, including paediatrics or related to autologous HSCT. The primary outcome will be the prevalence of oral medication adherence; the secondary outcomes will be the risk factors of MNA, the interventions aimed at increasing medication adherence and the outcomes of MNA. Two researchers will independently screen the eligible studies, then extract and describe the data. Disagreements will be resolved by a third researcher. We will provide a qualitative narrative synthesis of the findings.

Ethics and dissemination Ethical approval is not required given that previously published studies will be used. We will disseminate the findings through conference presentations and publications in international peer-reviewed scientific journals.

PROSPERO registration number CRD42022315298.

INTRODUCTION

The number of haematopoietic stem cell transplants (HSCTs) is increasing worldwide, with 48 512 transplants in the year 2019, including 19 798 allogeneic transplants (41%) in Europe,¹ and 23 768 HSCTs in the

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The review will examine six databases and grey literature, leading to a broad synthesis of the available evidence regarding medication adherence among adult recipients of an allogeneic haematopoietic stem cell transplant.
- ⇒ The review will include primary studies without language and time restrictions, allowing the maximum inclusion of studies published in the field.
- ⇒ Studies with low methodological quality will be excluded, thus ensuring rigour and robustness in the findings of the review.
- ⇒ The independence of the researchers in the selection, analysis and summary of the studies will ensure rigour and strengthen the findings of the review.
- ⇒ According to the expected heterogeneity across studies, a quantitative synthesis of the results in the form of meta-analysis may not be possible.

USA, of which 9498 (40%) were allogeneic.² Patients who receive an HSCT must take a complex oral medication regimen based on prophylactic and immunosuppressive treatment.^{3–5} Thus, patients may encounter difficulties managing the high number of tablets, which may vary over time due to medication prescription changes.⁶ However, a high level of adherence to this very complex regimen is required to avoid infections and to minimise the risk of other complications, such as graft-versus-host disease (GvHD) or disease relapse.⁷ It is well known that adherence plays a key role during and after the HSCT, increasing survival, and medication non-adherence (MNA) is closely associated with GvHD.^{4, 6, 8, 9}

Adherence is defined by WHO as ‘the extent to which the patient follows medical instructions’.¹⁰ It is composed of three phases: initiation (starting the prescribed medication intake), implementation (the agreement between a patient’s actual dosing compared with the medical prescription) and persistence (the length of time between



the first dose and last dose taken).¹¹ Differently, the term 'compliance' implies patient passivity^{12, 13}; therefore, the adherence concept and term was considered as a point of reference in this study.

The adherence rate in developed countries is about 50% among patients with chronic illness.¹³ To the best of our knowledge, the only systematic review available regarding medication adherence among recipients of an HSCT was published by Morrison and colleagues in 2017.⁷ Authors included five studies: two in adults,^{14, 15} one in both children and adults¹⁶ and two in paediatric population.^{6, 17} The estimated adherence to oral therapy in that review was between 33% and 94.7%⁷ and it has been reported to decline over time among adults,^{15, 16} except for Chieng *et al*,¹⁴ who reported an improvement in medication adherence over time. More recently, a prospective survey conducted by Ice and colleagues⁴ showed that out of 200 patients, 51% of them were not adherent to non-immunosuppressant medications, and 37.9% were not adherent to oral immunosuppressants. In a cross-sectional multicentric study enrolling 203 French adult recipients of an allogeneic HSCT, the MNA rate was 75%.¹⁸ In addition, in a secondary analysis of long-term survivors after an allogeneic HSCT, the authors reported an MNA prevalence rate of 68.7% to immunosuppressants.⁸

Various methods have been used to assess medication adherence, which can be categorised into subjective, objective or biochemical measures.¹² Among the first category, self-reported questionnaires (ie, the Compliance Evaluation Test,¹⁸ the modified Self-Efficacy for Appropriate Medication Use Scale,¹⁹ the Immunosuppressant Therapy Adherence Scale⁴ and the Morisky Medication Adherence Scale^{4, 7}) have been used. Among the objective measures, the electronic Medication Administration Record¹⁹ and the prescription refill records⁴ have been adopted by researchers, while among biochemical measures, the serum drug-level measurements of immunosuppressants, alone²⁰ or in combination, have been used.⁴ According to the available evidence, the use of self-report approaches combined with objective methods has been recommended^{7, 12, 13} to prevent heterogeneity in prevalence rates across studies.²¹ Moreover, it has been recommended to report when adherence is measured, the medications prescribed and the conceptual definition of adherence considered by researchers to increase the methodological quality of studies.²¹

WHO¹³ has classified reasons for poor medication adherence in chronic illnesses into five categories: socioeconomic factors, health system/healthcare team-related factors, disease-related factors, therapy-related factors and patient-related factors. Among individuals who have undergone solid transplantation, several factors have been investigated regarding their association with MNA.³ At the patient-related level, some studies have documented the role of psychosocial factors^{9, 22} by using the Stanford Integrated Psychosocial Assessment for Transplant (SIPAT) recipients, previously validated in the population who had received a solid organ transplant,^{22, 23} and the Transplant Evaluation

Rating Scale (TERS) as a pretransplant screening instrument to predict mortality, medication adherence and GvHD occurrence. Patient age,⁴ education,²⁴ distress⁴ as well as the efficacy of the caregiver(s)²⁵ have also been investigated. At the therapy-related level, the long-term duration of the therapy²⁵ and the higher number of daily immunosuppressant pills have been studied.⁸ However, as has emerged from a published systematic review⁷ and recommended by the Patient-Centered Outcomes Working Group of the National Institutes of Health in 2015,²⁶ future research is warranted to understand the facilitators and barriers of medication adherence.

Interventions to improve medication adherence have only been investigated to a limited extent, and to our best knowledge no summary of the available studies has been published. Specifically, a recent French retrospective study²⁰ has assessed the effectiveness of pharmaceutical consultations on the adherence to oral immunosuppressive therapy. The intervention was performed by a hospital pharmacist to patients who had received an allogeneic HSCT (n=26) the day before discharge from the bone marrow transplantation centre (BMTC) and from 2 to 4 weeks after discharge. There were no significant findings in favour of the intervention group on medication adherence. In their quasi-experimental study, Polito *et al*¹⁹ compared medication counselling by a pharmacist and self-management with nursing supervision until discharge to a control group among 51 recipients of an allogeneic HSCT. There were no differences between the two groups regarding medication adherence, although at discharge the experimental group had higher median knowledge scores. Moreover, evidence regarding different educational strategies, such as peer education or the involvement of patients as trainers, has not yet been summarised.

The effects of medication adherence on clinical outcomes, such as infections, GvHD, disease relapse and mortality, are emerging in the literature.^{4, 8, 9, 20, 22} Mishkin *et al*²² reported no significant associations between SIPAT ratings and survival; however, patients with a high-risk SIPAT score had an increased risk of being admitted to the intensive care unit (ICU). Similarly, no differences emerged in survival between adherent and non-adherent patients in the prospective survey by Ice and colleagues,⁴ nor with respect to acute GvHD and infections in the quasi-experimental trial by Charra *et al*.²⁰ On the other hand, there was a difference in the development of mild chronic GvHD among non-adherent patients compared with adherent patients.⁴ While pretransplant screening with the TERS has been documented to contribute to prediction of survival after HSCT, the TERS score did not correlate with the Medication Experience Scale for Immunosuppressants (MESI)—used as an adherence measure—suggesting that mortality is not associated with MNA.⁹ There is a need to summarise the evidence regarding clinical outcomes to discriminate between adherence and non-adherence behaviour and to identify patients at increased risk²¹ and in need of tailored interventions.

Studies regarding oral medication adherence prevalence, its associated factors, the effectiveness of interventions promoting it and the associated clinical outcomes among the adult recipients of an allogeneic HSCT are sparse and date back to recent years.^{4, 7–9, 18–20, 22} Therefore, this review is intended to provide a comprehensive and quality-assessed summary of studies to inform clinical practice and to address further primary research. The findings will also increase the awareness of patients and their caregivers regarding MNA and its consequences, allowing them to act at any modifiable risk factors with targeted interventions. Our primary aim is to summarise the available evidence regarding the phenomenon of oral medication adherence among adult recipients of an allogeneic HSCT based on prevalence rates and data collection tools used to measure it. Our secondary aim is to summarise the evidence regarding the predictors and risk factors of MNA, the effectiveness of interventions to promote medication adherence and the clinical outcomes influenced by MNA, as documented in primary studies to date.

METHODS AND ANALYSIS

We have registered the present protocol in the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42022315298) on 8 April 2022. This protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (see online supplemental table 1).²⁷ The review process will be completed within 6 months of protocol registration, and the systematic review will be reported following the updated PRISMA statement.²⁸

Eligibility criteria

We will consider all primary studies to be eligible for the review, ensuring the following elements as defined with the Population, Intervention, Comparison and Outcomes and Time framework, as recommended by the Joanna Briggs Institute (JBI) methodology²⁹:

- ▶ *Population*—adult (aged ≥ 18 years) patients who have undergone allogeneic or haploidentical HSCT and must take oral medication in the post-transplant phase, after discharge from BMTCs, regardless of the number of pills prescribed.
- ▶ *Intervention*—all kinds of interventions aimed at increasing medication adherence delivered from any healthcare providers (HCPs), during hospitalisation in the BMTCs and/or in the post-transplant phase, as an outpatient or remote follow-up.
- ▶ *Comparison*—usual care (ie, consultations, counselling, peer education and/or no comparison group).
- ▶ *Outcome(s)*—primary outcome describing the prevalence of oral medication adherence to immunosuppressant and non-immunosuppressant medications among the selected population after the discharge from BMTCs. The secondary outcomes are: (a) risk factors, barriers and predictors, and possibly related

MNA assessment tools; (b) effectiveness of interventions aimed at increasing medication adherence; and (c) infections (bacterial, viral and fungal), acute and chronic GvHD, hospital readmission rate, disease relapse and overall survival, as associated with MNA.

- ▶ *Time*—from transplantation to 4 years post-HSCT, according to the longest median follow-up among the available studies.⁸

Inclusion and exclusion criteria

Our target population consists of adult patients who have undergone allogeneic or haploidentical HSCT, for any transplantation indications, and must take oral medications (both immunosuppressants and non-immunosuppressants, such as prophylactic medications) in the post-transplant phase.

We will include all published and unpublished primary studies: (a) on humans, from inception until 10 May 2022; (b) written in any language; (c) experimental (randomised and non-randomised), observational (prospective, retrospective cohort and case-control), correlational, cross-sectional and longitudinal, in addition to case series and case reports; and (d) with a low risk of bias, according to the quality assessment findings.²⁹ Therefore, we will exclude secondary studies, qualitative studies, study protocols, case series and case reports and publications without original data (ie, comments, letters to the editor and editorials) or including the paediatric population (<18 years old) or relating to autologous HSCT. In addition, we will exclude studies where adherence does not relate to medication (ie, diet regimen, physical exercise).

Primary and secondary outcomes

The primary outcome of the review is the oral medication adherence rate. We will adopt the theoretical framework proposed by WHO,¹³ where adherence is defined as ‘the extent to which a person’s behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider’. However, the focus of adherence will be the medication regimen, thus excluding ‘a diet, and/or executing lifestyle changes’ because they are not in line with our research aims. To measure the medication adherence rate, we will investigate subjective (ie, self-report questionnaires), objective (eg, prescription refill records) or biochemical measurements (serum drug levels).¹²

The secondary outcomes of this review are the following:

- a. Risk factors, barriers or predictors of MNA as measured with tools.
- b. Interventions increasing medication adherence (ie, full description, frequency of provision and duration, comparator).
- c. Clinical outcomes as associated with MNA, such as the incidence rates of bacterial, viral and fungal infections; the incidence rates of acute and chronic GvHD³⁰; hospital and ICU readmission prevalence rates; disease relapse rates; and overall survival rates. We will assess

correlations or associations, if any, between medication adherence/MNA and patient-reported outcomes (ie, health-related quality of life, symptom experiences and patient satisfaction).³¹

Information source

We will access the following databases: the Cochrane Library, Cumulative Index of Nursing and Allied Health Literature (CINAHL), EMBASE, MEDLINE via PubMed, PsycINFO and Scopus. An initial search in the PubMed database will be performed by the first researcher (CV) to identify keywords and Medical Subject Headings (MeSH) appropriate to the aims of the review. Then, the search strategy will be refined and tested by the other researchers (IM, AP). Thereafter, the search string will be inserted into the other databases.

We will also search for grey literature, including dissertation theses and reports, protocols or guidelines from international scientific societies regarding medication adherence in the HSCT population. We will screen the reference lists of the included articles and the excluded systematic reviews using a hand search, to identify additional sources. If the full text of a study is not available, we will contact the authors directly. In the case of studies written in languages other than English, Italian and German, all accessible by authors, we will employ native translators to provide an English translation.

Search strategy

Different search strings have been designed and applied, considering the primary outcome and the three secondary outcomes. The date of the last update of the literature search was 10 May 2022. The final search strategies for the six selected databases, with MeSH terms and keywords, are shown in online supplemental table 2. No filters and/or limits have been used.

Data management and selection process

We will download citations retrieved from the six electronic databases and import them into software (EndNote®) that will facilitate the study selection process, with automatic identification and exclusion of the duplicates.

After the removal of duplicates, the first researcher (CV) will screen article titles and abstracts according to the inclusion and exclusion criteria; then, another researcher (IM) will independently screen the articles, reaching a consensus on eligible studies to include in the review. Disagreements between the researchers will be solved using consensus and consultation with a third researcher (AP), who will not have participated in the screening phase. A full-text assessment will then be performed by two researchers (CV, IM) independently, and then with common agreement with the third researcher (AP). The lists of references from the studies will also be screened, with the aim of retrieving and adding relevant studies, following the inclusion criteria. We will present the selection process in the PRISMA flow chart.²⁸

Data collection process

A pilot grid will be created in Microsoft Word® to extract data for at least 10% of the included articles, conducted independently by the first (CV) and second (IM) authors. After the pilot test, changes will be included if necessary, and the final chart will be developed, where study data will be reported and double-checked. Discrepancies in data extraction by the researchers will be discussed until a consensus is reached, with the supervision of a third researcher (AP).

An example of information that will be extracted from each study could be:

- ▶ Main characteristics (author(s), publication year, country, study design, study setting, study duration).
- ▶ Main and secondary study aims(s).
- ▶ Population profile, such as the number of participants, median age, gender distribution, race, ethnicity, socioeconomic status (where available), haematological disease due to HSCT, type of allogeneic HSCT, time from HSCT and name of oral medication(s), categorised into immunosuppressants or non-immunosuppressants.
- ▶ Main results of the study according to the primary and the secondary outcomes of the review:
 - Risk factors, predictors, barriers (description), by also describing the tools used to assess the risk of MNA.
 - Intervention(s) to improve medication adherence (description of the intervention, timing and provider(s) of the intervention(s), comparator).
 - Outcomes (ie, incidence rate of bacterial, viral and/or fungal infections, acute and/or chronic GvHD, hospital and/or ICU readmission rate, disease relapse rate and/or overall survival rate) and time from HSCT (in days) to assess them.

Risk of bias

We will perform a risk of bias assessment of all the individual studies included. The assessment will be performed independently by two researchers (CV, IM), and conflicts will be solved by a third researcher (AP).

The assessment will be based on the use of the JBI appraisal checklists,²⁹ according to the study design of the included studies. The JBI has different checklists for each study design (ie, randomised controlled trials, quasi-experimental, cohort). An example is the critical appraisal instrument for studies reporting prevalence data that will be used to assess the risk of bias of cross-sectional studies, which assesses the appropriateness of inclusion criteria (target population, sampling and sample size), the description of participants and the setting, the use of valid and reliable measurement of the studied condition, the use of appropriate statistical analysis and the assessment and management of adequate response rate.³²

There are four possible responses for each item: 'yes', 'no', 'unclear' or 'not applicable'. The overall appraisal for each included study will consist of 'seek further info' or 'include' or 'exclude' the study from the final

inclusion.²⁹ Therefore, studies assessed as excludable will not be considered in the data synthesis and a brief comment explaining the reason for the exclusion will be indicated. We will provide a table reporting the results of the risk of bias assessment for each included study.

Data synthesis

Two researchers (CV, IM) will independently summarise the findings, including only those studies considered eligible after the risk of bias assessment. First, the main study features will be summarised by reporting, for example, the origin country of the authors, the study aims and design, its duration, the sample size and the participants (ie, age, gender, ethnicity, education, type of HSCT). Then, a qualitative narrative synthesis of the results will be provided; specifically, the findings that emerge will be synthesised in four dimensions, according to the primary and the three secondary aims of this review. For example, the prevalence rates reported in the studies for immunosuppressant and non-immunosuppressant medications will be presented with the minimum, maximum and median values. The data collection methods, the description of risk factors of MNA and the interventions applied to improve adherence will also be summarised.

Regarding the investigated prevalence and outcomes, due to the expected different medication adherence measures and interventions across studies,⁷ the heterogeneity of the identified studies may prevent the ability to conduct a meta-analysis. However, if the data allow, two researchers (CV, IM) will independently investigate the heterogeneity of the studies using the I^2 statistic.

Confidence in cumulative evidence

We will assess the quality of the evidence by using the Grading of Recommendations Assessment, Development and Evaluation framework³³ for both primary and secondary outcomes. 'High', 'moderate', 'low' and 'very low' are the levels that will be used to assess the strength and quality of the evidence regarding the identified outcomes. The evaluation will be performed independently by two researchers (CV, IM), and an expert researcher (AP) will resolve any disagreements.

Patient and public involvement

None.

ETHICS AND DISSEMINATION

Because the study will only be based on published and retrievable literature, no ethics approval is required. We will submit the findings of our systematic review to international peer-reviewed scientific journals based on the identified primary and secondary outcomes. Furthermore, we will disseminate a summary of the systematic review through professional meetings and conference presentations, to promote implementation in HCP practice, such as providing screening tools to recognise

patients at risk, barriers and risk factors of MNA or interventions to improve medication adherence.

DISCUSSION

We aim to summarise the available studies regarding the phenomenon of oral medication adherence by means of prevalence rates, predictors and risk factors of MNA, the effectiveness of interventions to support it and outcomes associated with MNA among the HSCT population. Although we will employ a systematic approach and search an extensive number of databases, a publication bias might occur. Moreover, the expected heterogeneity across studies regarding their measures, tools and interventions⁷ might prevent a quantitative synthesis of the results. Furthermore, the external validity of the findings will be only for adult population: we decided to exclude the paediatric population because of the differences in psychological answers to the disease and medication posology²¹ and to the influence of the child–parent dyad on medication adherence.^{7,25} In addition, facilitators and barriers could be different between the paediatric and the adult population.⁷

The findings will be of interest to various stakeholders, including HCPs (such as nurses, haematologists and psychologists working in BMTs and in the follow-up setting), patients who have received an HSCT, their caregivers and their representatives. Although disease relapse remains the leading cause of mortality among patients after receiving an HSCT, a substantial improvement in survival and a reduction of complications have been reported over the years.³⁴ Therefore, also considering the increase in the incidence of GvHD,⁸ medication adherence has become a priority in designing and delivering healthcare interventions during and after HSCT.^{4,6,8,9}

Complications and failure of transplant during hospitalisation have mostly been attributed to biological reasons.⁹ There has been a recent increase in attention towards medication adherence among patients who have received a transplant, especially in the case of early discharge and after, in the outpatient follow-up. Therefore, the findings will increase the information available to HCPs, patients, their caregivers and representatives in understanding the factors hindering or promoting medication adherence. Moreover, this review will inform HCPs regarding the most effective interventions capable of promoting medication adherence by considering all factors involved—from those related to the complexity of the therapy to the uncertainty and psychological distress experienced by the patients and their caregivers.³⁵ Providing data on the phenomenon of medication adherence might increase the awareness of HCPs regarding the educational needs during hospitalisation and over time, because not all BMTs have reference HCPs in charge of transitional care. Moreover, providing evidence might increase the opportunities to benchmark the data at each centre with that accumulated in the literature and appropriately summarised. Finally, the findings of this review may also

reveal possible gaps in the HSCT literature and highlight research questions to address with primary studies.

Contributors CV and AP conceptualised the protocol. CV wrote the protocol. IM and AP methodologically and critically revised the protocol. CV is the guarantor of the review. All authors have contributed, read and approved the final protocol.

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