Noncompliance with immunosuppressive regimen in organ transplantation : Is it worth worrying about ?

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Introduction

Transplantation is a valuable option for end stage kidney, heart and liver disease (e.g. RTX : 1-2 ; e.g. HTX : 3 ; e.g. LTX : 4-5). However, transplantation needs to be regarded as chronic condition. According to the World Health Organization (WHO), 'chronic diseases' are defined as : *"diseases which have one or more of the following characteristics : they are permanent, leave residual disability, are caused by non-reversible pathological alteration, require special training of the patient for rehabilitation, or may be expected to require a long period of supervision, observation or care"* (6).

Because transplantation is a chronic condition, transplant management needs to integrate psychosocial and behavioural interventions in addition to state of the art medical treatment. Compliance with the therapeutic regimen is a central component of the behavioural dimension of transplant patient's chronic disease management. Compliance (synonyms : adherence, concordance) is defined as : *"the extent to which a person's behaviour corresponds with the agreed recommendations from a health care provider"* (6-8).

The life-long therapeutic regimen of the organ transplant recipient is complex, including life-long medication regimen (including immunosuppressive drugs), infection prevention, smoking cessation, following alcohol guidelines, following dietary guidelines, regular exercise, and attending to regular clinic visits.

Ample evidence shows the negative impact of behavioural factors such as noncompliance with the immunosuppressive drugs and lack of smoking cessation on subsequent clinical outcome in organ transplant populations (6,9-12).

Understanding the behavioural dimension of transplant patients' management refers to information on prevalence, determinants and consequences of noncompliance as well as the discussion of compliance enhancing interventions.

Prevalence of noncompliance with the immunosuppressive regimen

Prevalence of noncompliance with immunosuppressive drugs in solid organ transplantation ranges between 20-25%, depending on the case finding methods, measurement methods, and operational definitions used (e.g. REVIEWS : 9-15 ; e.g. RTX : 16-34 ; e.g. HTX : 17,34-42 ; e.g. LTX : 17,43-47). It is important to notice that (non)compliance in liver transplantation is still under-investigated. Only one study to our knowledge has explored noncompliance with the immunosuppression in liver transplantation (48).

Measurement methods of medication noncompliance

Direct measurement methods (e.g. observation and assay) as well as indirect measurement methods (e.g. self-report, pill count, clinical judgement, collateral report, and electronic event monitoring) can be used to assess the prevalence of (non)compliance. Advantages and disadvantages of direct and indirect measurement methods have been described in detail elsewhere (49). Self-report and collateral report underestimate noncompliance (11,49). Only electronic monitoring (EM) allows the visualization of individual medication taking dynamics (49). EM is the most sensitive method to assess noncompliance to date (50).

Consequences of noncompliance with the immunosuppressive regimen

Consequences of noncompliance with immunosuppressive regimen can be evaluated from a clinical (REVIEWS : e.g. 9-12 ; e.g. RTX : 15-16,18-20,22-23,26-29,51-56 ; e.g. HTX : 39,57 ; e.g. LTX : 46,50,58) and an economic perspective (REVIEW : e.g. 59 ; e.g. RTX : 60-61 ; e.g. HTX : 35). Noncompliance with immunosuppressive medication has been associated with an increased incidence of acute rejections, graft loss and mortality (REVIEWS : e.g. 9-12 ; e.g. RTX : 15-16,18-20,22-23,26-29,51-56 ; e.g. HTX : 39,57 ; e.g. LTX : 46,50,58) and with a decreased quality of life (e.g. RTX : 62 ; e.g. HTX : 63-65 ; e.g. LTX : 66).

International Symposium – 20 Years of Liver Transplantation at Cliniques Universitaires Saint-Luc. Brussels (Belgium), April 23, 2004.
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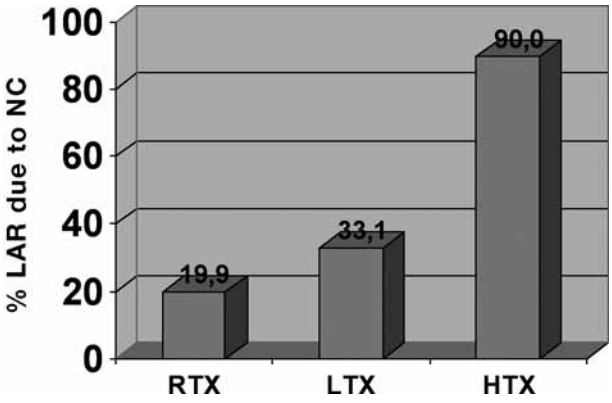
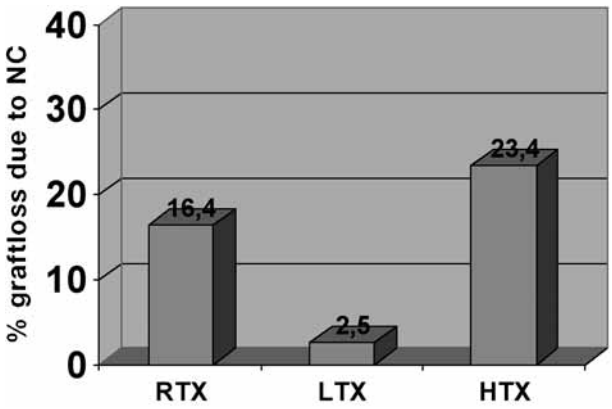


LAR : Late acute rejection (i.e. > 1 year post transplantation) (RTX :17,26-27,51 ; HTX : 17,26-27,38 ; LTX : 17,26-27,46, 68-69).

Fig. 1. — Weighted mean of late acute rejections associated with noncompliance in adult renal transplant, liver transplant and heart transplant patients.



(RTX : 18,20,23-24,28,54,56,70-77 ; HTX : 17,67,78 ; LTX : 58).

Fig. 2. — Weighted mean of graft loss associated with noncompliance in adult renal transplant, liver transplant and heart transplant patients.

Clinical consequences of noncompliance with the immunosuppressive regimen

In order to explore the impact of noncompliance with immunosuppression on clinical outcomes after transplantation, we summarized all available evidence in the literature exploring noncompliance as a possible etiological factor in the occurrence of late acute rejections and graft loss after solid organ transplantation. Most evidence is from the renal and heart transplant population, the liver transplant population is less studied. We calculated the weighted mean of noncompliance as an etiological factor in the occurrence of clinical events for each organ transplant type (see figure 1 & 2).

Between 20% and 90% of the late acute rejections can be linked to noncompliance (RTX : 17,26-27,51 ; HTX : 17,26-27,38 ; LTX : 17,26-27,46,68-69) (see figure 1). The weighted mean for noncompliance associated to graft loss ranged from 2.5% in liver transplantation to 23.4% in heart transplantation (RTX : 18,20,23-24,28,54,56,70-77 ; HTX : 17,67,78 ; LTX : 58) (*) (see figure 2).

Noncompliance was the third leading cause of mortality in heart transplantation. These findings were based on a single centre report reanalysing the proportion of deaths associated to noncompliance as initially reported by UNOS. Where initially only 2% of the deaths were reported to be caused by noncompliance, detailed chart review showed that this proportion was actually 13%, making noncompliance the 3rd leading cause of patient mortality in this sample (78).

Most studies exploring noncompliance as an etiological factor in the occurrence of clinical events only grasp the tip of the iceberg as they only include patients experiencing a clinical event. In order to grasp the whole iceberg and to substantiate the effect of subclinical noncompliance on subsequent clinical outcome, prospective cohort studies studying patients irrespective of clinical outcome, provide the strongest evidence to understand the impact of noncompliance as a risk factor for poor outcome.

To our knowledge, only 4 prospective cohort studies have been performed so far in adult solid organ transplant populations, i.e. 2 in heart transplantation (39,67) and 2 in renal transplantation (22,79). Two of these studies investigated the impact of noncompliance in the first year post-transplantation, showing that noncompliance negatively impacts clinical outcome (RTX : 22 ; HTX : 39) and two focused on late post-transplant noncompliance (i.e. >1 year post-transplantation) (RTX : 79 ; HTX : 67). Both early and late noncompliance are associated with poor clinical outcome (RTX : 22,79 ; HTX : 39,67).

Late noncompliance was assessed in 101 heart transplant patients using electronic event monitoring. Patients were followed up prospectively for a 5 year period. Noncompliance showed a significantly shorter clinical event free time (i.e. composite outcome of late acute rejection, retransplantation, transplant vasculopathy, and/or patient death) after 5 years follow-up (67). After controlling for known predictors for poor post transplant outcome, the adjusted relative risk for poor outcome was twofold, indicating that noncompliance doubles the risk for a negative clinical outcome (67). Another prospective cohort study in renal transplantation in which late noncompliance was assessed using self-report, found a higher rate of late acute rejections and poorer renal function at 5 years follow-up in noncompliant patients (79).

(*) In renal transplantation, there was one outlier, which was not included in the calculation of the weighted mean, because the chosen operationalization of noncompliance was not mentioned (75).

Economic consequences of noncompliance with the immunosuppressive regimen

In addition to clinical consequences, the effects of noncompliance can also be evaluated economically. We performed a full economic evaluation of noncompliance with immunosuppressive therapy after renal transplantation, modelling the total costs as well as the life-time outcomes in terms of QALY's (Quality Adjusted Life Years) between compliant and non-compliant patients (80).

Findings showed that compliance is more costly over a lifetime. The higher lifetime costs in compliant patients, however, can be explained through to the higher life-expectancy of compliant patients relative to non-compliant patients (16 versus 12 years). This study however also demonstrated that outcome expressed in QALY's was higher in compliers. Our approach allowed us to calculate the scope for compliance-enhancing interventions. The incremental cost per QALY of compliance relative to non-compliance was estimated at € 35,021/QALY (80). The economic appropriateness of compliance enhancing interventions depends on the maximum societal willingness to pay for a QALY and the cost per QALY associated with the compliance enhancing intervention. When the societal willingness to pay for a QALY equals or exceeds € 35,021/QALY, there is scope for compliance enhancing interventions (80).

The cost per QALY of the compliance-enhancing intervention will be determined by the strategy chosen : intervening in all patients or only in those identified at risk for non-compliance. The latter option will turn out to be cheaper if it can be performed in an efficient way, i.e. by identifying noncompliers using valid and reliable measurement tools (i.e. electronic event monitoring) or by using clusters of risk factors that are associated with a high probability for noncompliance. Understanding these risk factors is therefore crucial for effective transplant patient management. Moreover, established modifiable determinants of noncompliance provide also the basis for developing compliance enhancing interventions (80).

Determinants of noncompliance with the immunosuppressive regimen

According to a literature review recently published by the WHO (6), determinants or correlates of noncompliance can be categorized in 5 groups : 1. socio-economic factors, 2. patient related factors, 3. condition or disease related factors, 4. therapy or treatment related factors, and 5. health care system and health care team related factors, respectively.

Patient related factors have been most explored, health care team and health care system related factors less, clearly indicating a bias in the literature seeing the patient as the defaulter. Most studies on determinants of noncompliance are performed in the renal and heart transplant populations.

Socio-economic risk factors for noncompliance with immunosuppression regimen refer to age (i.e. adolescence), economic factors (e.g. cost of medication) and social factors (e.g. lack of social support, family instability, social isolation) (e.g. in RTX : 17,24,26-27,30,81 ; e.g. in HTX : 17,26-27,36 ; e.g. in LTX : 17,26-27,44).

Patient related variables found to be associated with noncompliance in solid organ transplant populations are cognitive impairment, functional and sensorial limitations (e.g. impaired vision, hearing deficits), low self-efficacy with medication taking, knowledge deficit, inadequate health beliefs (e.g. believing that patients with a living related donor need less immunosuppression) and a low perception of vulnerability to complications (e.g. rejections and graft loss). Previous noncompliance has also been associated with current and future noncompliance (e.g. in RTX : 16-17,23-30,55,81 ; e.g. in HTX : 17,26-27,36,38,82 ; e.g. in LTX : 17,26-27,44,50,83).

Condition related factors found to be associated with noncompliance in transplantation are depression, substance abuse and absence of symptoms (e.g. in RTX : 19,29-30,55,81).

Treatment related factors that have been demonstrated to be associated with an increased risk for noncompliance are complexity of treatment regimen (e.g. number of drugs and doses prescribed), longer duration of the treatment (life-long medication taking), and patient's perceptions associated with side-effects of the immunosuppressive medication (e.g. cosmetic side-effects such as excessive hair growth, moon face) (e.g. in RTX : 19,29-30,55,81).

A recent report of the WHO (6) underscores the importance of health care system and health care team related factors as determinants of noncompliance. The number of health care system / health care team related factors with regard to noncompliance investigated in the solid organ transplant population is however limited. Determinants of noncompliance substantiated include e.g. an authoritarian communication style of the health care worker, lack of knowledge of the health care worker concerning (non)compliance, and time constraints during clinical consultations. (e.g. in RTX : 24-25,28,84 ; e.g. in LTX : 85).

Importantly, noncompliance needs to be seen as an epiphenomenona. Several possible determinants, correlates or risk factors of noncompliance with immunosuppression regimen can contribute to patients not correctly taking the immunosuppressive drugs in organ transplant populations. Diverse dynamics can lead to noncompliance. Understanding these risk factors and dynamics in individual patients is a first step to identify possible options for tailored compliance enhancing interventions.

Compliance enhancing interventions

Effective compliance enhancing interventions have been shown to be high dose, multilevel, and applied over a longer period of time (6,86-92). Importantly, educational interventions alone are not effective to improve compliance (86-92). It is the combination of educational, behavioural and social support interventions that is most promising in increasing the likelihood of medication compliance (86-92). Most suggested interventions are aimed to target the patient. Yet, increasing evidence shows that also the system of care should be adapted to optimise compliance interventions (6).

To our knowledge, only one RCT testing the effectiveness of a compliance enhancing intervention in identified noncompliers, has been performed in adult renal transplant recipients (University of Basel). This study showed that a 3 months high-dose, multi-level interventions increases compliance (i.e. SMART trial) (93, De Geest *et al.*, work in progress).

Parallel with tailored patient interventions targeting modifiable determinants and integrating evidence from RCT's, attention should also be given to interventions targeting the system level, i.e. implementing core systems tuned towards chronic disease management as mentioned before.

Compliance enhancing interventions

Educational interventions improve knowledge, but do not guarantee behavioural change (86-92,94-97). Education focuses on factual knowledge transfer related to medication-taking related aspects (e.g. intended effect of medication, medication administration, potential side-effects, as well as problem solving strategies). Patient education will be most effective if it is adapted to the cognitive, developmental and intellectual capacities of the individual patient. A combination of oral and written information using a stepwise approach is preferred. A formal evaluation will help to determine if the patient has understood the information correctly. The use of computed assisted learning tools seems to be a promising tool for standardized patient education (e.g. OTIS® - Roche Pharmaceuticals).

In addition to educational strategies, interventions with the goal to increase compliance should also include behavioural strategies. Interventions aiming at increasing self-efficacy with medication taking and self-management of different aspects of the therapeutic regimen, have been shown to be effective (86-92,98-103). Further, the treatment should be simplified as much as possible. Other options include the use of medication aids (e.g. pill boxes and reminders), tailoring (i.e. adapting the regimen into the patient's life style) and cueing (i.e. taking the medication in combination with routine behaviours, such as tooth brushing, or at meal time).

A last set of strategies used to improve adherence, are social support interventions (86-92,96,104). Involvement of family members in the patient's treatment plan (i.e. preparing medication, reminding the patient to take medication, redeeming prescriptions), and the building of a trustful relationship between the patient and the health care worker, have all been described to improve compliance behaviour (86-92,96,104).

Transplantation is a chronic condition, that renders acute care models inappropriate to address transplant patients' health needs and to achieve optimal outcomes. Chronic disease management models, as they inherently integrate psychosocial and behavioral aspects of the patient's management, have the potential to affect patients' medication adherence behavior. The main challenge is to integrate adherence enhancing interventions in transplant patients' management, as the previously mentioned acute care paradigm in transplant follow-up can not provide the time to focus on behavioral aspects. Moreover, it should be guaranteed that knowledge and skills to perform behavioral interventions are available in transplant teams (6).

Recommendations for future research

In order to strengthen the behavioural dimension of transplant patient's management, following aspects need to be further explored and addressed in future research. The prevalence and consequences of noncompliance with the immunosuppressive regimen, needs to be re-explored as newer immunosuppressive regimens are used in patients. Exploration of determinants / correlates / risk factors for nonadherence should also include health care team and health care system related factors. The area of nonadherence with immunosuppressive regimen in liver transplantation should be further explored, given the relative lack of evidence in this area. Studies focusing on prevalence, determinants and consequences of noncompliance with immunosuppressive regimen should use electronic event monitoring for compliance measurement, as this is the most sensitive method to date. Finally, there is a need for RCT's testing the effectiveness of compliance enhancing interventions. Outcomes tested should be adherence as well as the impact of these interventions on clinical outcome.

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