

## The Challenge of Assessing Adherence to Subcutaneous Biological Drugs in Immune-Mediated Inflammatory Diseases. Letter to the Editor Regarding Michetti P, Weinman J, Mrowietz U, et al. *Adv Ther* (2017);34:91–108. doi:10.1007/s12325-016-0441-3

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Dear Editor,

Lack of adherence to medications is frequent in chronic diseases and has important implications with regard to health outcomes, including an increased risk for poor clinical outcomes, mortality, and greater health care costs [1–3]. As a high percentage of non-adherent patients are intentional, a strong belief in the necessity of the prescribed drug, outweighing potential concerns about side effects or long-term effects, is essential to increase adherence. In the recently published ALIGN study [4], Michetti et al. reported non-adherence rates to anti-TNF-alpha drugs of approximately 20–40% based on the four-item Morisky Green questionnaire. Furthermore, they found an association between patient adherence and the Beliefs about Medicines Questionnaire (BMQ) scores: in particular, higher BMQ-specific necessity

score was associated with better adherence in the six immune-mediated inflammatory diseases (IMID) studied [i.e., rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis, Crohn's disease, and ulcerative colitis], whilst for the BMQ-specific concerns score an inverse association (higher BMQ-specific concerns score with poorer adherence) was found in patients with RA, AS, and PsA.

These results made us reflect about the need to optimize patient education, but also on how to improve the assessment of adherence to biological medications in particular, given the high economic impact related to IMID and their treatment with these drugs. Specifically we are very interested in research on how to measure adherence to subcutaneous (SC) biological medications—typically self-administered—and how to improve adherence. Moreover, the identification of patients with risk of becoming non-adherent over time is also essential to allow early implementation of preventive actions.

In the ALIGN study, the assessment of adherence to anti-TNF-alpha drugs was done using the four-item Morisky Green questionnaire. The Morisky Green test was developed and validated to measure non-adherence to oral medications and is widely used for this purpose [5]; however, is the Morisky Green test on its own an adequate tool to measure adherence to SC biological drugs? We recently published the

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results of a retrospective study on adherence to SC biological drugs in patients with RA, the ARCO study [6]. In this study, we assessed adherence during the first 12–16 months of therapy after prescription of a new SC biological drug. Non-adherence was assessed by the Medication Possession Ratio, [MPR, (number of days actually covered by the medication administered by the patient/number of days of the study period to be covered by the medication prescribed)  $\times$  100], with non-adherence defined as MPR no greater than 80%. Hospital pharmacy registries were the source to calculate the number of days covered by the medication taken by each patient. In addition, investigators also inquired about adherence with the four-item Morisky Green questionnaire during the study visit, whose wording was adapted to focus on SC biological drugs.

The percentage of non-adherence according to the MPR was 14.3% (95% CI 11.1–18.3). The Morisky Green questionnaire classified 76.7% of patients as highly adherent and 23.3% as non-adherent to the SC biological medication (22.7% as moderately adherent, 0.6% as low adherent). Responses to each item of the Morisky Green questionnaire focused on the SC biological drug are displayed in Table 1. Although the percentage of agreement between the Morisky Green and the MPR in the classification of adherence was 73.3%, the kappa coefficient showed only a slight agreement ( $\kappa = 0.142$ ), with low positive predictive value for non-adherence. Of note, 32 of 273 patients

(11.7%) who were classified as highly adherent by the Morisky Green had been non-adherent according to the MPR, whilst 75.9% of those classed as moderately/low adherent by the Morisky Green were adherent according to the MPR. One limitation in our study is that the Morisky Green questionnaire was administered only once, at the study visit, and recall bias could have conditioned the results. On the other hand, the MPR allows the identification of non-adherent patients only retrospectively, which is also a limitation in clinical practice. The point we want to raise is that, although a useful tool, using only the Morisky Green questionnaire seems insufficient to correctly identify non-adherence to SC biological drugs, and complementary strategies are needed.

There have not been many studies assessing adherence to prescribed SC biological medications in patients with IMiDs. In general, these studies have relied on administrative databases, which do not take into account individual patients' situations, such as periods of drug discontinuation due to adverse events or surgeries, or changes in the administration interval [7]. Other studies have used the Morisky Green questionnaires [4, 8] or direct questions on the last dosage administered [9] to evaluate adherence to the SC medication.

The MPR, when it can be calculated thoroughly, like in our study, is a good measure of adherence to SC biological drugs, but with two limitations: first, and most important for clinical practice, the MPR allows only a retrospective assessment of adherence; it verifies lack of adherence when it happened, but is not valid for early detection of non-adherent patients, or for identifying patients at risk of non-adherence. For this purpose, inquiring about the patients frequently with direct questions that help us detect behaviors at risk for non-adherence (such as those in the Morisky Green questionnaire) is necessary, but because the Morisky Green does not detect non-adherence to SC biological drugs with the same precision as non-adherence to oral treatments (and the clinical implications can be different), a regular tracking of the medication taken or used by the patients is necessary. This will allow further investigation and early intervention if

**Table 1** Responses to each Morisky Green item in the ARCO study (number and percentage)

Do you ever forget to inject your SC medication? (% yes)	38 (10.6%)
Do you administer your SC medication at the scheduled date? (% no)	17 (4.8%)
When you feel better, do you stop administering your SC medication? (% yes)	3 (0.8%)
At times, if you feel worse, do you stop administering your SC medication? (% yes)	40 (11.2%)

non-adherence is suspected. The second limitation is that although patients collect the SC medication from the pharmacy, it does not necessarily imply that they are administering the doses correctly or on the scheduled days. The MPR will not detect non-adherence in patients who inject their medication irregularly, providing they inject it within the time frame spanning from the collection of vials to the next collection from the pharmacy. When patients get their SC medications injected in health care institutions (either primary care or hospitals), it is easier to track medication use, but most patients self-inject the SC drug at home. In this situation, reminders or diaries in which patients can register the injection dates might be useful, although not 100% indicative of what patients have actually done [10]. Monitoring drug levels has been proposed as a helpful tool to manage biological drugs, especially in patients with inflammatory bowel disease [11]. Although not routinely, measuring drug levels could also help in making decisions in several circumstances, e.g., in certain patients with worsening disease and undetectable or very low drug levels, the possibility of non-adherence to medication should be explored before switching to another biological drug [12].

Whilst several interventions have proven efficacious for increasing adherence to short-term treatments, interventions for improving adherence to chronic therapies have been less successful [13]. Thus, any effort to prevent patients from discontinuing adherence to biological drugs should be useful in the long term. From this perspective, the BMQ [14], with or without other tools or questionnaires, namely the Brief Illness Perception Questionnaire (BIPQ) [15], also used in the ALIGN study, might be useful as screening tool to identify those patients at higher risk of becoming non-adherent. Perhaps, a first instance to use the BMQ-general should be when a person becomes a chronic patient who will need continuous treatment over the years. At that moment, the BMQ could aid by highlighting the specific fears or behaviors that shape the patient profile, thus guiding the implementation of specific actions or educational activities. Regular use of the

BMQ-specific and other questionnaires, especially when changes in the therapy are needed or side effects occur, could be useful to guide personalized efforts to reassure patients about their therapies.

In conclusion, assessing adherence to SC biological medication is a challenge, and it is likely to require information from several sources. A validated strategy to diagnose non-adherence to SC biological drugs is needed. The items on the Morisky Green questionnaire help in identifying patients with behaviors leading to poor adherence, but a thorough tracking of all the medication collected by patients is essential to address deviations. Moreover, measuring drug levels could also be useful when non-adherence is suspected but cannot be confirmed otherwise. Besides, the BMQ is a good tool to understand patients' beliefs about medicines, and to aim to establish individual strategies targeted to strengthen beliefs in the necessity of therapy, and to reduce concerns, which will in turn reduce the risk of non-adherence to the prescribed medications. Studies to confirm this hypothesis are needed.

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**Compliance with Ethics Guidelines.** This article does not contain any new studies with human or animal subjects performed by any of the authors.

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