

Adherence to Therapy in Patients with Idiopathic Inflammatory Bowel Diseases on Subcutaneous Biological Therapy

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Abstract

Introduction: Non-adherence is a problem in the treatment of chronic diseases including idiopathic inflammatory bowel diseases (IBD) and, according to the literature, adherence is insufficient in a quarter of patients. This results in a risk of therapy failure and relapse. This factor plays a significant role in self-administration of subcutaneous biological therapy (BT). The objective of the paper is the evaluation of adherence of IBD patients on subcutaneous BT who were monitored conventionally in comparison with the use of telemedicine monitoring means.

Methodology: Adherence was evaluated on the basis of retrospective data of a single centre regarding the frequency of visits and the medication dispensed to patients registered on the IBD Asistent platform involving active sending of notifications with reminders to administer the medication and calculating the Medication Possession Ratio (MPR). The control group consisted of conventionally monitored patients comparable in terms of the treatment type, diagnosis, sex and age. A secondary primary point was the serum levels of the medication in the subpopulation of patients treated with adalimumab.

Results: The study involved 69 patients on subcutaneous BT, active in the period from July 2022 to July 2023 on the IBD Asistent platform. Matched to this group at a ratio of 2:1, there was a control group of 138 conventionally monitored patients. The average age of the patients was 40.6 ± 11.1 years, 43.5% of the patients were men. Crohn disease was diagnosed in 83.1% patients. 91.3% of patients were treated with adalimumab, 7.2% of patients received subcutaneous vedolizumab, and 1.5% of patients were treated with golimumab. The median monitoring time was 517 days. The adherence evaluated by means of MPR was high both in the telemedicine and conventional groups (0.960 ± 0.084 vs. 0.967 ± 0.094 ; $p = 0.6123$). The rate of non-adherent patients with MPR below 0.86 was 8.8% and 8.0%, respectively ($p = ns$). In the whole patient population, the adherence was significantly lower in women and a tendency towards higher adherence was seen in patients with ulcerative colitis. The age of patients played no role. Among patients with low levels of adalimumab, the rate of non-adherent patients was considerably higher (36.8% vs. 4.9%; $p = 0.0002$).

Conclusion: Although the overall adherence to a subcutaneous BT is relatively high and independent of the method of patient monitoring, MPR evaluation may help identify risk groups of patients. Low levels of the medication result from non-adherence in a third of the cases.

Keywords: *Idiopathic Inflammatory Bowel Diseases (IBD); Biological Therapy (BT); Medication Possession Ratio (MPR); IBD Asistent Platform*

Introduction

Non-adherence to the prescribed treatment is a long-term problem of treatment of chronic diseases, the significance of which grows with the growing rate of chronic diseases in the overall morbidity of the population. To describe the problem, the World Health Organization uses the term non-adherence to treatment and characterizes it as a silent epidemic, as it is an estimated cause of 21 - 37% of adverse events that are associated with treatment and may be prevented [1]. The consequences include an increased rate of treatment failure, hospitalization and growth of costs for healthcare systems. Given that the estimated rate of inadequate adherence reaches as much as 50% in advanced countries, it is a significant and underrated problem [2]. Idiopathic inflammatory bowel diseases are not an exception. The number of patients treated in the Czech Republic for IBD diagnoses is currently estimated to be around 70 thousand, and the incidence remains in comparison with global data very high [3]. Given the steady increase of prevalence, due to either the actual increase of incidence or better diagnosing, and the proportion of patients receiving expensive centre-based treatment, the ability to measure, evaluate and increase adherence is an important element of patient care.

A basic pharmacotherapeutic means for the treatment of inflammatory bowel diseases after failure of a conventional therapy, and increasingly an early therapy in the form of a top-down approach as well, is an innovative treatment including monoclonal antibodies and small molecules, where TNF-alfa antibodies still dominate, especially in the first line. Despite very good efficiency in a large proportion of patients, the annual rate of primary failure and secondary loss of response is approximately 15% of patients, which considerably limits this type of treatment [4]. Apart from pharmacodynamics causes, a dominant cause is the pharmacokinetic failure conditioned by the development of antibodies to the medication, the development of which may be potentiated by excessive fluctuation of the medication concentration in the body or by long-term low serum levels [5]. The stability of levels depends on a regular administration of the medication, which is - particularly where subcutaneous forms of treatment with a short administration interval are concerned - conditioned by an adequate adherence of patients.

Aim of the Study

The paper aims to evaluate the adherence of patients with Crohn disease and ulcerative colitis receiving subcutaneous forms of biological therapy in the environment of a tertiary centre and to assess the impact of patient monitoring by telemedicine means on the adherence rate.

Methods

The primary monitored population consisted of IBD patients registered on and actively using the IBD Asistent platform at the Clinical and Research Centre for Idiopathic Inflammatory Bowel Diseases ISCARE. It is an online interface which may be used by any patient stable on a biological therapy over a long term for communication with the centre and, when filling out a health questionnaire, also for substituting a part of follow-up outpatient visits [6]. A total of 1122 patients were registered on the platform at the time of the data processing. The preconditions for inclusion into the retrospective evaluation included active participation on the platform in the period from July 2022 to July 2023, treatment by a subcutaneous form of a biological therapy that remained unchanged throughout the period, and receiving electronic notifications from the system as reminders to administer the medication, which is an optional feature of the registration for the platform. The control group was a cohort of conventionally monitored outpatients who were matched to the group monitored by telemedicine means in the ratio of 2:1 on the basis of their sex, age, diagnosis, and treatment type.

Adherence was evaluated by using the Medication Possession Ratio (MPR), which is calculated as the number of days for which the patient was dispensed the medication divided by the number of days in the actual interval in which the patient arrived to be dispensed next doses of the medication. The data on the number of dispensed injection syringes, dose, administration interval and visits in the centre were obtained from the hospital information system. MPR was always calculated from the first to the last recorded date of visit in the centre when the patient was dispensed the medication. The threshold value assessed as non-adherence was set to be $MPR < 0.86$.

In patients treated with adalimumab, serum medication levels measured by means of a blood test at each visit were also recorded. If at least 2 serum levels were available, the patients were included in the sub-analysis of relation between serum levels and MPR.

The Mann-Whitney test was used for the comparison of groups, while categorical values were evaluated by the Fisher exact test, and a regression analysis was used for the evaluation of a relation between MPR and age. GraphPad Prism (version 10.3.1) software was used for the analysis. The significance level was set as $p < 0.05$.

Results

The preconditions for inclusion in the study were fulfilled by 74 patients. Following the sample analysis, 3 patients receiving ustekinumab were removed from the study because this medication is usually administered right in the centre due to the long administration interval, and 2 patients were removed because of erroneous recording of the treatment type (Figure 1). Of 69 patients included in the study, 30 (43.5%) were men and 39 (56.5%) were women with an average age of 40.5 years. Most of the patients were treated for Crohn disease (84.1%). Adalimumab was administered to 63 patients, 5 patients were treated with vedolizumab, and 1 patient was treated with golimumab. The control group included 138 conventionally monitored patients (Table 1). The patients who were included in the study in the study period of 12 months until July 2023 continued to be monitored until data acquisition or until a change of the medicinal product. The median time of monitoring was 517 days.

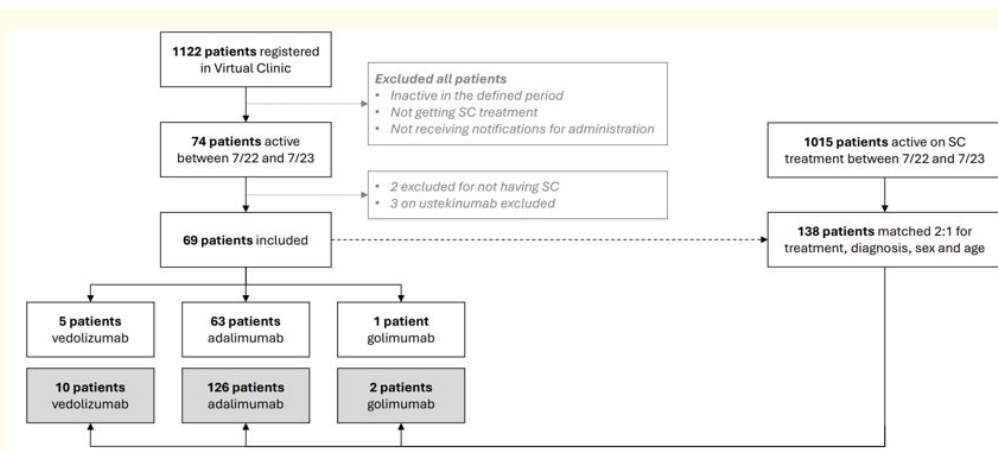


Figure 1: Algorithm of patient selection for monitoring.

	IBD Asistent n = 69	Conventional monitoring n = 138	
Age (years)	40.51 ± 11.01 [21-74]	40.63 ± 11.12 [20-76]	p = ns
Sex			p = ns
- Men	43.5% (30/69)	43.5% (60/138)	
- Women	56.5% (39/69)	56.5% (78/138)	
Diagnosis			p = ns
- Crohn disease	84.1% (58/69)	82.6% (114/138)	
- Ulcerative colitis	15.9% (11/69)	17.4% (24/138)	

Treatment type			p = ns
- Adalimumab	91.3% (63/69)	91.3% (126/138)	
- Vedolizumab	7.2% (5/69)	7.2% (10/138)	
- Golimumab	1.5% (1/69)	1.5% (2/138)	

Table 1: Characteristics of the study population at the time of inclusion in the monitoring; average ± standard deviation [minimum-maximum].

The average value of MPR for the entire study period was 0.9596 (standard deviation (SD) ± 0.0843) in the group monitored by telemedicine means, and 0.9665 (SD ± 0.0941, p = 0.6123) in the conventionally monitored cohort. There was no significant difference between the groups (Figure 2). The total proportion of non-adherent patients in the telemedicine group was 8.8% in comparison with 8.0% in the conventional group (p = 0.7917).

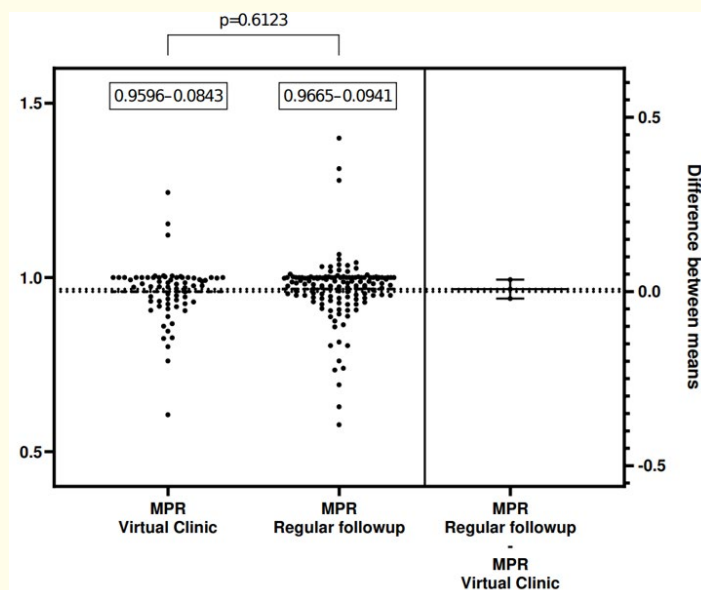


Figure 2: Comparison of MPR in patients monitored by telemedicine means and conventionally; MPR: Medication Possession Ratio, Virtual Clinic - telemedicine group, Regular followup - conventionally monitored group; average ± standard deviation.

Since the groups were comparable in terms of both the baseline characteristics and MPR, we also evaluated a potential impact of the diagnosis on adherence in the entire study population. A numerically lower level of adherence was seen in patients with Crohn disease in comparison with ulcerative colitis, but the difference was not statistically significant (0.9573 ± 0.0854 vs. 0.9831 ± 0.1004 , p = 0.1468). When evaluating the relation between the patient’s age and MPR, no connection between the age and adherence based on MPR was proved (Figure 3).

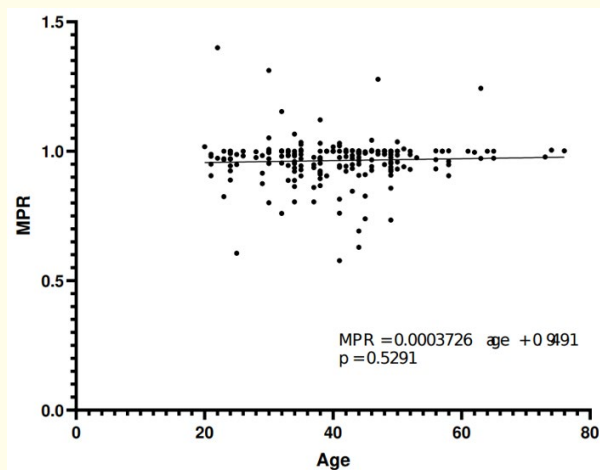


Figure 3: Relation between MPR and the patient’s age; MPR: Medication Possession Ratio.

However, a difference was seen when comparing the populations of men and women, with a statistically significantly lower adherence in the group of women (0.9510 ± 0.1003 in women vs. 0.9808 ± 0.0743 in men, $p = 0.0211$) (Figure 4).

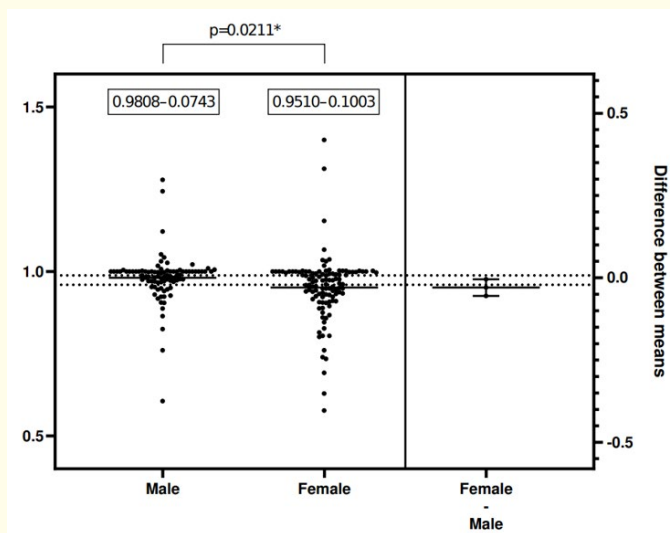


Figure 4: Comparison of MPR in the populations of men and women; MPR: Medication Possession Ratio; average \pm standard deviation.

A sub-analysis evaluating serum levels included 61 patients monitored by telemedicine means and 122 conventionally monitored patients treated with adalimumab. The average serum adalimumab levels were comparable in both groups ($9.39 \pm 4.07 \mu\text{g/ml}$ vs. $9.14 \pm 4.28 \mu\text{g/ml}$, $p = \text{ns}$), just like the proportion of patients with an intensified dose or shortened administration interval (36.1% vs. 33.6%, $p = \text{ns}$) (Table 2). Given the identical MPR values, serum levels and proportion of patients in an intensified regimen, we also

evaluated the relation between the serum levels and MPR in the entire group of patients treated with adalimumab. In patients who did not meet the criterion of adequate adherence (MPR < 0.86), the average serum adalimumab levels were considerably lower than in patients with good adherence, despite the fact that a considerably higher proportion of patients with low adherence had an intensified administration regimen (5.65 ± 4.73 µg/ml with a low MPR vs. 9.54 ± 4.02 µg/ml with a high MPR, p = 0.001) (Table 3). Likewise, when evaluating the rate of adherence on the basis of serum adalimumab levels, it was found out that in the group of patients with very low adalimumab levels (< 3.5 µg/ml) there was a significantly higher proportion of subjects with insufficient adherence to the treatment than in the group showing sufficient trough levels of adalimumab (36.8% vs. 4.9%, p = 0.0002) (Table 4).

	IBD Asistent n = 61	Conventional monitoring n = 122		
Serum levels of ADA	9.39 ± 4.07 [0-18.4]	9.14 ± 4.28 [0-22.0]	p = ns	
Proportion of patients with intensified regimen	36.1% (22/61)	33.6% (41/122)	p = ns	
- Serum levels (intensified regimen)	10.09 ± 5.38 [0-18.4]	9.03 ± 5.63 [0-22.0]	p = ns	p = ns
Proportion of patients with standard dosing	63.9% (39/61)	66.4% (81/122)	p = ns	
- Serum levels (standard dosing)	8.99 ± 3.12 [4.1-17.3]	9.19 ± 3.44 [0-17.2]	p = ns	

Table 2: Average serum levels of adalimumab in patients monitored by telemedicine means and conventionally (µg/ml), and proportions of patients with intensified regimen; average ± standard deviation [minimum-maximum]; ns: Non-significant.

	Serum levels of adalimumab (µg/ml)	Proportion of patients with intensified regimen
Low adherence (MPR<0,86)	5.65 ± 4.73 [0-15.4]	80.0% (12/15)
Good adherence (MPR≥0,86)	9.54 ± 4.02 [0-22.0]	30.4% (51/168)
	p = 0.001	p = 0.0002

Table 3: Average serum levels of adalimumab, and proportions of patients with intensified regimen according to the rate of adherence; average ± standard deviation [minimum-maximum].

	Patients with low adherence	Patients with sufficient adherence	
Low ADA levels (< 3.5 µg/ml)	36.8% (7/19)	63.2% (12/19)	p = 0.0002
Adequate ADA levels	4.9% (8/164)	95.1% (156/164)	

Table 4: Proportion of patients with insufficient adherence in relation to the serum levels of adalimumab; ADA: Adalimumab.

Discussion

The paper retrospectively evaluated adherence of patients with idiopathic inflammatory bowel diseases receiving subcutaneous biological therapy to the regular administration of the medication, depending on the method of patient monitoring and the demographic data, and the relationship between pharmacokinetics and adherence in the sub-population of patients treated with adalimumab.

To evaluate adherence, it is possible to use subjective methods on the basis of information provided by the patient regarding the quantity of taken medication or derived from questionnaires fulfilled by the patient, as well as objective values of medication levels or metabolite levels, or supervised administration of the medication as a direct form, and database records concerning dispensed or reported medications as an indirect method of adherence checking [7]. The MPR method used in this paper is a metric widely used due to its simplicity, in particular, and provides information about what part of the patient's visiting interval is covered by the dispensed medication. Data on the overall adherence of IBD patients to their treatment differ in the literature, with a wide range of non-adherence from 7% to 72% reported for oral medicinal products [8]. With respect to biological therapies from the group of anti-TNF α , an extensive review shows a pooled adherence rate of 82.6% with values ranging from 36.8% to 96% [9]. There is no agreement on a required rate of adherence; while the frequently stated value of 80% is considered acceptable by some clinical studies, it must not be lower than 95% according to others [10]. In one of the largest individual publications that evaluated adherence of more than 5000 patients to adalimumab therapy, an average cumulative value of MPR was calculated to be 0.94 and a cut-off value of MPR was set to be 0.86, as this value maximizes the difference between the adherent and non-adherent cohorts in terms of a risk of treatment failure in the form of corticoid prescription or necessity of hospitalization [11]. Due to the objectively set cut-off value based on the defined criteria and similar characteristics of the study group, the MPR value of 0.86 was also used as an adherence criterion in our cohort instead of a usual arbitrarily set limit of 0.8.

Our study included a total of 207 patients treated with various types of subcutaneous form of biological therapy in a single centre. Patients treated with ustekinumab were not included in the evaluation due to the long administration interval, because their injection is mostly administered by a health professional right in the centre. The published data show that administration of a biological therapy in a facility of the healthcare provider is an independent factor associated with 2.4-times higher adherence in comparison with self-administration of the medication [12]. The primary objective of the paper was to assess the impact of telemedicine monitoring on the adherence rate, with the assumption that a higher degree of active involvement of the patient in the treatment process together with notifications with reminders to self-administer the medication will result in improved adherence to the treatment. However, no significant difference in the adherence rate between the patients monitored by telemedicine means and the patients monitored by standard means was seen. One of the reasons is probably an overall very high calculated adherence of the entire study population, which exceeds MPR 0.96. Although the value is not considerably higher in numerical terms than the value stated in the study of Govani, *et al.* the proportion of non-adherent patients below the set cut-off in the aforesaid study exceeded 20%, while in our patient cohort it was only 8-9%. It may only be guessed what factors resulted in the high adherence rate of the study population, but a certain role may undoubtedly be played by the operating practice of the centre, including the manner and quality of keeping patient records and planning their visits. The risk factors of low adherence to self-administration of a biological therapy in the study of Shah, *et al.* included the diagnosis of Crohn disease, higher-line biological therapy, psychiatric disease history, tobacco and narcotics abuse, and a low socioeconomic status [13]. In other cases, a lower adherence rate was associated with a younger age of the patients, female sex, longer duration of the disease, use of alternative medicine methods, or subjectively reported obstacles, such as inconvenient administration, adverse events, forgetting, or health improvement [12,14-17]. Those data also correspond to our results. Other assessed factors included the impact of sex, age and diagnosis on the adherence rate, and while age was not associated with adherence, a significantly lower adherence rate was proved in the female population and, numerically in patients with Crohn disease, where no statistical significance was proved but one of the causes is the small size of the cohort of patients with ulcerative colitis which reduces the power of the test.

Association between adherence and serum levels was evaluated only in the population of patients treated with adalimumab. This group formed a dominant part of the study population, and conclusions on the impact of pharmacokinetics of vedolizumab and ustekinumab on the treatment effect are not completely conclusive or, at least, no minimum and optimum trough serum levels which should be achieved through therapeutic monitoring (TDM) were defined [18,19]. There was not any evaluable difference in the adalimumab serum levels between the group monitored by telemedicine means and the group monitored conventionally, not even in the patients with an intensified

treatment regimen whose proportion was comparable in both cohorts. Given the homogeneity of the study population, it was possible to use to set cut-off to evaluate the effect of MPR on serum levels in the entire population; the part of the study population with a low adherence rate showed significantly lower average levels of adalimumab in serum, despite the fact that the share of patients with an intensified treatment regimen was considerably higher in that group. Since the evaluation of adherence is not a common part of patient monitoring, a clinically more significant question was whether suboptimal serum levels may be associated with a low adherence rate. Here it was evident that while the group with optimum adalimumab levels showed a low proportion of non-adherent subjects below 5%, in the group with insufficient levels the non-adherence rate was almost 37%. Consequently, clinical implication is that when analysing the causes of non-optimum pharmacokinetics in the use of TDM in the event of self-administration, one of the main considered factors should be the patient's failure to respect the administration interval.

Interventions proposed in order to achieve a higher rate of adherence include repeated education of patients regarding the importance and mechanism of action of the administered medication, risks of treatment failure, and manifestations of adverse events resulting from irregular administration. Others include alterations to the formulation, quantity and mechanism of medication administration leading to more comfortable injection administration, optimization and centralization of the system of preventive monitoring of patients and, last but not least, behavioural interventions including greater involvement of patients in the decision-making process and their stimulation to administer the medication regularly, e.g. by introducing electronic telemedicine means. They may lead to both cost savings and higher patient satisfaction and awareness of the issues related to the patient's disease [20].

Conclusion

In the context of published results, adherence to a subcutaneous biological therapy in our study population is high and independent of the form of patient monitoring. However, MPR evaluation allows to identify groups of patients who are likely to show lower adherence as well as individual non-adherent patients at the risk of treatment failure. In more than a third of cases, insufficient serum adalimumab levels were associated with non-adherence, and this factor has to be considered when evaluating the pharmacokinetics.

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