

How do You Like the Pen? Patients' Opinion About Switching Adalimumab From Prefilled Syringe to Pen in Inflammatory Bowel Disease

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ABSTRACT

OBJECTIVES: Inflammatory bowel diseases are lifelong illnesses and have a huge impact on the quality of life and workability. Although the fully human anti-tumor necrosis factor-alpha, adalimumab provides great opportunity to use biological therapy at home, application of the prefilled syringe might be difficult for some. The **aim** of this study was to evaluate patients' opinion about the newly introduced adalimumab prefilled pen compared to the prefilled syringe.

METHODS: Our questionnaire based survey focused on the degree of difficulty of the usage, any inconveniences and the proportion of self-injection for each mode of administration.

RESULTS: The questionnaire was filled by 101 patients (female/male: 49/52). Patients applied adalimumab therapy for 33 months on average and changed from the prefilled syringes to the prefilled pen for 4 months on average. Sixty-six % of those who used the prefilled syringe administered adalimumab themselves. Self-administration of injections caused difficulties for 19% of patients, and 15% of patients had serious aversion to self-administration. On the other hand, in case of the prefilled pen, 94% of patients administered adalimumab themselves. Self-administration caused difficulties for only 5% of patients, and just 1% of patients reported aversion to self-administration ($p < 0.001$). Overall 70% of patients assessed the change positively, and they reported significantly less (23.6% vs 9.3%; $p = 0.009$) inconvenience with administration.

CONCLUSION: Our multicenter study including more than hundred inflammatory bowel diseases patients revealed that switching from

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the prefilled syringe to pen results in higher self-administering rate, significant reduction in pain and in local reaction at the injection site.

Key words: Crohn disease; Ulcerative colitis; Adalimumab; Syringe; Pen; Self-administration

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INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic, relapsing, multiorgan conditions with unknown aetiology and decreased quality of life (QoL). Growing knowledge about the aetiology led to therapeutic breakthrough during the last decades in IBD. Targeted biological agents against TNF-alpha (tumor necrosis factor-alpha) proved to be the most effective treatment option even in the most challenging and complication associated cases. Infliximab, adalimumab and golimumab are the approved anti-TNFs for the treatment of different forms of IBD. Administration of these agents is markedly varied and adalimumab is the only one which is administered via subcutaneous (SC) injection using either a prefilled syringe or an autoinjection pen. Both devices are single-use, disposable, prefilled and adequate for self-administration. The autoinjection pen contains 40 mg adalimumab in 0.8 mL solution, like the prefilled syringe and was approved by the US Food and Drug Administration (FDA) based on a safety and bioavailability study comparing the syringe and the autoinjection pen in 295 healthy volunteers^[1]. Self-administered injectable medications have some advantages of portability, flexible scheduling, and lower costs over intravenous infusions, however the risk of non-adherence is higher and problems relating to injection technique may occur in certain patients^[2], furthermore, not all patients are physically able to inject themselves. Non-adherence is considered as a major problem among patients with chronic, incurable disease, and the World Health Organization claimed in 2003 that improving patient adherence to long-term therapies would be more beneficial than any other intervention^[3]. Autoinjection pens have been shown to be preferred over syringes by patients requiring long term SC administration of medications in other chronic conditions, like diabetes mellitus, migraine, and growth hormone deficiency^[4]. Concerning the administration of adalimumab by two different ways, by two single-use injection devices, up to now two studies were performed in rheumatoid arthritis (RA) with relatively low number of patients. Both of them confirmed that patients preferred the pen versus the traditional prefilled syringe because they found it easier to use and to felt less pain during the administration^[5,6]. However, patients with RA differ from patients with IBD in the age and the RA associated functional limitations which are uncommon among younger IBD patients and results in difficulties in subcutaneous self-administering. Therefore the objectives of our multicentre study were to evaluate patients' opinion about the newly introduced adalimumab prefilled pen compared to the prefilled syringe.

PATIENTS AND METHODS

This was a prospective, multicentre, questionnaire-based observational study carried out in eleven Hungarian IBD centres. All patients diagnosed with ulcerative colitis (UC) or Crohn's disease (CD) enrolled in the study were treated with adalimumab and changed syringe to autoinjection pen so they had enough experience with both methods. The study design was a simple observational study, the switch was performed independently after Abbvie started to market autoinjection pen formulation instead of syringe at November 2016 in Hungary.

Adult patients diagnosed with UC or CD, who have had experiences with both forms of adalimumab, performed the questionnaire-based survey anonymously. Inclusion criteria were also age over 18 years, IBD diagnoses based on symptoms, radiological, endoscopic, and histological findings at least three months prior to the study. All patients were selected voluntarily. Patients who did not meet the above-mentioned inclusion criteria were excluded. All of the patients were on a 40 mg subcutaneous maintenance adalimumab therapy in every other week and had experiences with both form of adalimumab subcutaneous injection; the prefilled syringe and the prefilled autoinjection pen.

Online and paper-based surveys were performed. The survey was based on the differences between the prefilled syringe and the prefilled autoinjection pen; questions were about the difficulty of administration, inconveniences with administration with each form of adalimumab. Specifically, the patients had to rate the difficulty of administration in a visual analog scale (VAS, easy to use = 1 to very difficult to use = 10) and to write comments on their own words. The questionnaire contained questions for patients' demographic data (gender, age, patients' highest educational level and occupational status), IBD characteristics (year of diagnosis, phenotype, concomitant medication - previous biological therapy. Further questions of the questionnaire are in Appendix 1.

Statistics

Statistical analysis was performed using R Commander statistic programme, χ^2 -test, Sign-test, McNemar-test, Marginal homogeneity-test, Mann-Whitney-test and Fisher-test in collaboration with statisticians. Baseline characteristics and other categorical data were summarized using means. An "exact" 95% confidence interval (CI) was performed to compare patients who preferred the pen with patients who preferred the prefilled syringe. All statistical tests were performed at the 0.05 level of statistical significance.

Ethical approval

This study was approved by the Clinical Research Coordination Center University of Szeged Faculty of Medicine Albert Szent-Györgyi Health Center. Number of ethical licence: 4005.

RESULTS

A total of 101 patients were enrolled in our multicenter study. The baseline characteristics of the patients are reported in Table 1. Fifty-two men and 49 women were enrolled in the study; mean age at the time of the survey was 37.6 ± 11.3 years. Seventy-seven point two % of the patients were diagnosed with CD and 16.2% with UC. Mean duration of adalimumab treatment was 33 months (2-108 months) and the mean duration of autoinjection pen treatment was 4 months (1- 12 months).

Appendix 1. How do you like the autoinjection pen? Patients' opinion about the new mode of administration of adalimumab.

- 1) Since when are you on Humira therapy?
- 2) Were you treated with different type of biological therapies before Humira?
- 3) Did you hear about Humira before your therapy began?
- 4) If yes, from where did you hear about Humira?
 - Another physician
 - Nurse
 - IBD patient/organisation
 - Pharmacist
 - Own information seeking (Internet)
 - Other:
- 5) Which was the most important aspect you choose Humira therapy?
 - My physician recommended it
 - The subcutaneous mode of administration
 - Self -injecting at home
 - It is time saving
 - Other biological therapy was ineffective for me or I had an allergic reaction before
 - Other
- 6) What is your opinion about the effectiveness of Humira?
 - I am satisfied with it, I do not have any symptoms.
 - Basically I am satisfied with it, but I have remnant symptoms.
 - I am not satisfied with it, I think this treatment does not work.
- 7) What is your opinion about the administration of the traditional prefilled syringe form of Humira?
 - I gave it to myself, it was practical and easy to use.
 - I gave it to myself, but sometimes I had trouble with the administration technique.
 - I had aversion to inject it to myself so somebody else gave it.
- 8) Please indicate the difficulty of the administration of the Humira injection on a visual analog scale (1 to10).
- 9) Did you have any inconveniences with the administration of the traditional syringe form of the Humira injection?
- 10) If yes, please write down what kind of inconveniences did you have?
- 11) How long do you use the Humira ® Pen?
- 12) Was the autoinjection pen administration form an important feature choosing Humira therapy?
 - Yes, this is the reason why I chose Humira.
 - I chose Humira independently from the type of the administration.
 - I used Humira prefilled syringe before but now the Humira pen it is more convenient to me.
 - No, it is bother me that the administration form changed.
- 13) What is your opinion about the administration of the Humira® Pen?
 - I give it to myself, it is practical and easy.
 - I give it to myself but sometimes I have trouble with the administration technique.
 - I have aversion to give subcutaneous injection to myself, somebody else gives it.
- 14) Please indicate the difficulty of the administration of the Humira Pen on a visual analog scale (1 to10).
- 15) Did you have any inconveniences with the administration of the Humira®Pen?
- 16) If yes, please write down what kind of inconveniences did you have?
- 17) If you were switched from traditional prefilled syringe injection to prefilled, autoinjection pen, please specify your opinion about the switch.
- 18) If you think the pen is a better form of administration of Humira, please specify why.
- 19) Who picks up Humira prescription from the pharmacy generally?
 - 0 if always somebody else - 10 if always You
- 20) Do you use a transportcooler for the transportation of Humira injection?

Table 1 Baseline characteristics of patients.

Number of patients (N)	101
Females/males	49/52
Mean age (years; min-max)	37.6 (21-65)
Diagnosis type: CD/UC	78/17 (77.2% / 16.2%)
Mean disease duration at the time of survey (years; min-max)	11.5 (1-39)
Duration of adalimumab treatment (months; mean,min-max)	33 (2-108)
Duration of autoinjectionadalimumab pen treatment (months; mean; min-max)	4 (1-12)
Where did the patient hear about Humira	
doctor	-14 (13.8%)
nurse	-7 (6.9%)
IBD patient/organisation	-9 (8.9%)
pharmacist	0
own information seeking (Internet)	-13 (12.8%)
no answer	-58 (57.4%)
Educational status	
primary school	-7 (6.9%)
gymnasium	-7 (6.9%)
secondary vocational school	-44 (43.5%)
technical school	-10 (9.9%)
college, university	-30 (31.6%)
no answer	-3 (2.9%)

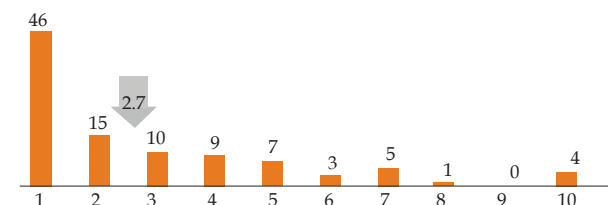


Figure 1 Degree of difficulty of the administration of Humira injection.

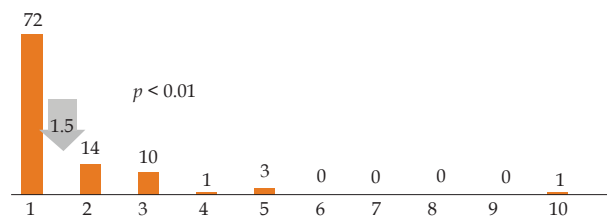


Figure 2 Degree of difficulty of the administration of Humira(R) Pen.

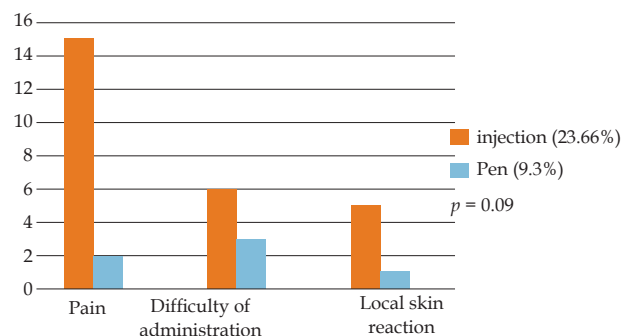


Figure 3 Did the patients have any inconveniences during the administration of Humira injection or Humira(R) Pen?

Sixty-seven of 97 (69.1%) patients chose adalimumab therapy because their doctor advised it, 27 (27.8%) patients because the previous biological therapy was ineffective or they had an allergic reaction previously and 3 (3.1%) because they found it to be easier to use and required less time to inject.

The majority of the patients (97/100; 97%) were satisfied with the effectiveness of the adalimumab treatment in general and only 3 % felt it ineffective. Forty-five of 78 (58%) CD patients and 4 of 17(23%) UC patients felt that their therapy is effective and all of the symptoms vanished ($p = 0.017$). According to our results the number of those patients who were satisfied with their therapy was significantly higher among CD patients. Examining the efficacy of adalimumab therapy we found that the previous other type of biological therapy ($p = 0.04$) and the type of the diagnosis (CD or UC, $p = 0.017$) affected significantly the feeling of effectiveness of the recent therapy ($p = 0.04$). After switching from the prefilled adalimumab syringe to the autoinjection pen the percentage of patients who gave the injection themselves increased from 66% (66 of 100 patients) to 95% (95 of 100 patients) ($p < 0.001$). Moreover, 19% of the patients found the prefilled syringe caused difficulties and 15% had serious aversion to administer it to themselves. In contrast with the subcutaneous injection form, 94% of the patients thought that the autoinjection pen is practical and easy to use and only 1 % had serious aversion to use it. In this study, the pen showed a statistically significant advantage regarding the mode of the administration, in the injection pain, and the difficulty of administration ($p = 0.05$).

Regarding preference, patients found significantly easier to inject pen over syringe. The mean (SD) visual analogue scale (VAS) score was 2.78 (2.37) for the syringe compared with 1.57 (1.26) for the pen ($p < 0.001$). Figure 1 and 2 shows the detailed data. In this study we found that the level of the difficulty of the administration the syringe or the pen was independent from the level of education. ($p = 0.268$ and $p = 0.587$). No association was shown between gender or type of diagnosis and the difficulty of the drug administration. Overall 70% of the patients assessed the switch positively, and they reported significantly less inconvenience with administration (23.6% vs 9.3%; $p = 0.09$) (Figure 3).

DISCUSSION

This was the first study examining the ease of use of prefilled adalimumab syringe and autoinjection pen in a large series of IBD patients. The previous data, coming from RA studies concerning that the administration of the pen is less painful over syringe, when the disease itself can cause functional limitations to subcutaneous self-administering and that is why the mode of administration can be more highlighted. Our study proved that autoinjection pen is more comfortable and more favour in the group of younger IBD patients without disability. The pen decreased the aversion from autoinjection from 15 to 1%, and while only 66% of the patients administered the syringe themselves before, 95% did it after switching to the pen. Educational level, gender and the type of the disease was not in association with the patients' opinion. After switching to the pen, patients reported significantly less pain and less local skin reactions, and felt significantly easier to inject.

The TOUCH study was the first examination in this topic involving 52 patients with RA in 2006. Although both studies (TOUCH and our) used different, self-made questionnaires, some of the results are highly comparable. Eighty-eight point five % of the RA patients preferred the pen in the TOUCH study; while 94% of the IBD patients thought that the autoinjection pen is practical and easy to

use while only 1% of the IBD patients had serious aversion with it^[5]. Overall, 70% of our patients assessed the switch to pen positively and only 9.3% of the patients felt any inconveniences regarding the pen.

Self-administering of the medication is one of the most important factors which increases patients' adherence and reduces excessive workloads in primary care. The study Borrás-Blasco *J et al.* about the acceptability of switching adalimumab from a prefilled syringe to an autoinjection pen examined this very important factor in 55 patients with different rheumatoid diseases. The percentage of patients self-administering medication increased from 51 to 84% in this study, while 66 to 95% in our study. The explanation of the higher level observed in our study can be the younger age (37.4 vs 50 years) of the IBD patients. Although this comparison may suggest that younger patients are braver to inject themselves, the introduction of a simpler and less uncomfortable autoinjection technique may increase the self-administering rate independently of the age of the patients. The mean visual analogue scale score was significantly lower after switching in both studies: 3.52 (2.26) for the prefilled syringe compared with 2.02 (2.16) for the autoinjection pen among patients with rheumatoid disorders and 2.78 (2.37) for the syringe compared with 1.57 (1.26) for the pen among IBD patients^[6].

To summarize, our multicenter study including more than hundred IBD patients revealed that after switching to pen from the prefilled syringe results a higher self-administering rate and significant reduction in pain and local reactions at the injection site. Our study provides new evidence to support the use of the adalimumab autoinjection pen in another group of patients with chronic disorders as previously observed in IBD.

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