

# Biological therapy and international travel: A questionnaire survey among Danish patients with rheumatic disease

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## Abstract

**Objective:** To describe travel activities, preparations, and health problems encountered by patients with arthritis receiving biological therapy.

**Methods:** A travel survey was conducted in a Danish rheumatology outpatient clinic by distribution of a semistructured questionnaire to 300 consecutive patients with arthritis.

**Results:** Among the 273 (91%) patients returning the questionnaire, a history of traveling outside Denmark was reported by 203 (74%) respondents and outside Europe by 92 (34%). In 81% of the patients, travel activities had not decreased after the initiation of biological treatment. However, 24% reported that they had become more cautious regarding the choice of travel destination. Pre-travel advice was sought by less than one-third of the patients, whereas travel insurance was taken out by 86%, but only half of them had disclosed information about the biological treatment. Treatment was discontinued temporarily while traveling in 26% of patients on subcutaneous biologics. The main reason for discontinuation was concern about transport and storage of medicine. Only 6% of the travelers had experienced health problems, which were of only minor importance.

**Conclusion:** Treatment with biologics seems not to have any major influence on international travel activity among Danish patients with arthritis. Health problems when traveling were of minor importance. However, pre-travel advice issues, including treatment compliance, transport of medicine, and insurance coverage, need to be addressed proactively by the outpatient clinic staff as part of patient consultation.

**Keywords:** Arthritis, biologic therapy, travel

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## Introduction

For more than 50 years, the treatment of autoimmune inflammatory rheumatic diseases (AIRD) has been based on use of steroids and disease-modifying antirheumatic drugs (DMARDs). The introduction of biologics since 1999 has revolutionized the therapeutic approach, particularly in patients with inadequate response to standard DMARDs. As a result, patients with rheumatoid arthritis, psoriatic arthritis, and spondylarthropathies today experience an improved daily functional level and quality of life, which allows them to work and also to travel for different purposes, including holiday, family visit, or business (1). However, different concerns and challenges related to chronic arthritis itself or to the treatment may prompt the patients to avoid traveling or change an otherwise preferred destination.

The number of international travelers has increased steadily in the past decades (2). Patients with underlying chronic diseases are also traveling more extensively in these years. In a 2014 Danish study, as many as 92% of patients with human immunodeficiency virus (HIV) infection reported travel activity outside Denmark despite different potential obstacles, such as HIV status on entry to certain countries, immune-deficiency-associated risk of infections, and the need of hand-carried medicine across the borders (3). Patients with arthritis may, in a similar manner as those with HIV, meet different obstacles when traveling, in particular to the part of transport and storage of subcutaneous biologics, which are administered by self-injections with intervals between twice weekly and once monthly. The biologics must be kept at a specific temperature range of 2°C-8°C, which requires a cooling box when traveling. The cooling element may cause problems for patients during the hand luggage scanning procedure if the liquid content exceeds the 100 mL limit, as stated in the international airport security regulations. Increased susceptibility to infections owing to the treatment with biologics may constitute another concern for the patients with arthritis when planning a travel arrangement (4).

Many countries are issuing recommendations to travelers regarding vaccinations prior to entry. The responses of vaccinations in patients with AIRD may be attenuated by the patient's biologic therapy, resulting in reduced vaccine effectiveness and protection. Moreover, there is also a potential risk of developing an active infection or severe adverse reactions with live virus or bacteria following vaccination, such as yellow fever (5-7). For this reason, specific recommendations have been incorporated for immunocompromised patients, such as patients with arthritis receiving biological treatment (8-10).

In this study, we aimed to assess the reported travel activities and preparations, such as pre-travel advice and travel insurance, in a questionnaire among Danish patients with arthritis treated with biologics. Health problems encountered during the travel were also addressed in the questionnaire.

**Methods**

This study was carried out in the rheumatology outpatient clinic at a Danish regional hospital during a 10-month period from March 2017 to December 2017.

More than 1,900 patients with rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, or spondylarthropathy were followed up in the clinic, and 400 of those patients were treated with biologics. Patients were registered in the

National Rheumatology Database in Denmark.

Treatment was provided free of charge to the patients. Infusions with biologics were given in the clinic with intervals of 6-45 weeks depending on the specific type of biological drug. Self-administered subcutaneous biologics are handed out as single-use prefilled syringes or pens for 2 months' consumption.

A total of 300 consecutive patients with arthritis receiving biological treatment were invited to participate in this study. A semistructured questionnaire was handed out to each study participant. The questionnaire was developed with inspiration from a questionnaire being developed and validated in conjunction with a similar travel survey among patients with HIV (3). This group of patients with HIV resembles those with rheumatic disease receiving biologics by having a chronic condition of underlying immunodeficiency. The questionnaire included 37 items within the following 7 main categories: socio-demographic data, treatment prior and during travel, history of travel, health insurance assignment, pre-travel advice seeking, and travel-related health issues. The survey was conducted using a cross-sectional design. The respondents were anonymous, but it was ensured by study participant registration that each respondent completed only one unique questionnaire.

This study was reported to the Danish Data Protection Agency (2008-58-0028). The regional committee of ethics did not require approval of this study. A written consent was obtained from all the participants.

**Statistical analysis**

Statistical analysis was performed using the Windows version of Microsoft Office Access database management system 2010; for pie chart analysis, the Microsoft Office World 2013 (Redmond, Washington, USA) was used. Categorical data were compared using the Chi-square test.

**Results**

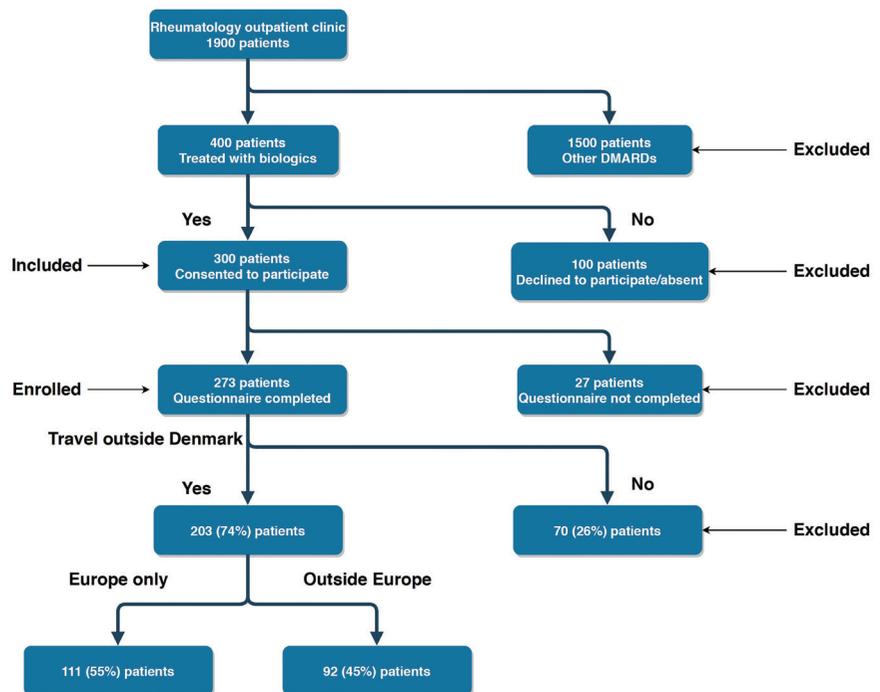
Among the 300 patients, who were invited for this study, 273 (91%) returned the completed questionnaire (Figure 1). Median age of the respondents was 57 years (range, 18-81 years).

**Travel activity**

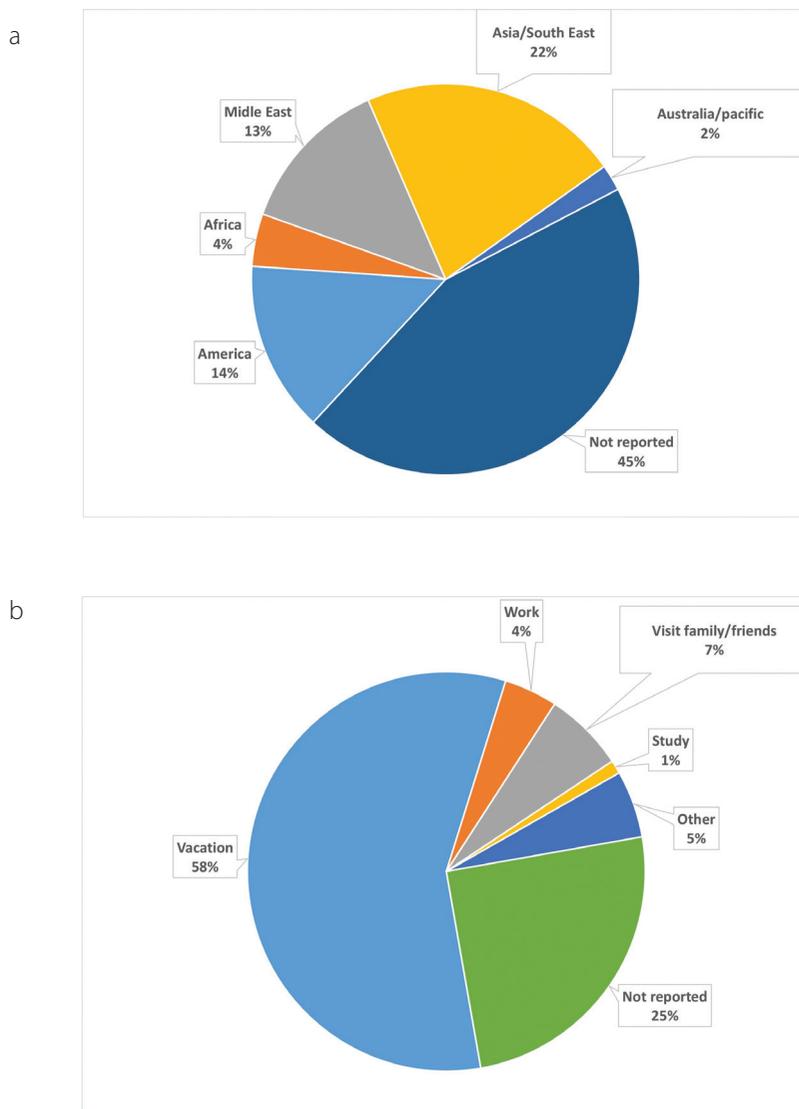
Travel outside Denmark after the initiation of biological treatment was reported by 203 (74%) patients; among these, 111 (55%) patients reported travel in Europe only, and 92 (45%) patients reported additional travel in other countries outside Europe (Figure 1). More than one-third (36%) of the 203 patients reported that the most recent travel had a duration of less than 1 week, while the remaining two-thirds reported a duration of more than 1 week. Figure 2 shows the distribution of trav-

**Main Points**

- Majority of Danish patients with arthritis continue the travel activity level after the onset of subcutaneous or intravenous biological treatment of their rheumatic disease.
- Less than one-third of this group of patients seek pre-travel advice; however, the informants expressed concerns regarding the potential implications of biological treatment, including travel immunization and insurance precautions, in addition to logistical challenges and customs regulations regarding the transport of hand-carried medicine across international borders requiring cold chain storage facilities.
- Treatment with subcutaneously administered biologics had been discontinued in one-quarter of the patients when traveling.
- A very small proportion of patients have experienced health-related problems in conjunction with travel, and those problems were only of minor importance.



**Figure 1.** Flowchart showing enrollment of study participants according to travel history.



**Figure 2. a, b.** Distributions of travel destinations (a) and travel purposes (b) among the 92 patients with a travel history outside Europe.

**Table 1.** Patient demographic and biologic administration characteristics in accordance with travel history.

	Total respondents N=273	Travel history	
		Yes n=203 (74%)	No n=70 (26%)
<b>Gender, n (%)</b>			
Men	127 (47)	95 (46)	32 (46)
Women	146 (53)	110 (53)	36 (51)
Median age, years (range)	57 (18-81)	57 (17-81)	55 (25-81)
<b>Administration route, n (%)</b>			
Subcutaneous	174 (64)	139 (68)	35 (50)*
Infusion	75 (27)	43 (21)	32 (46)*
Not reported	24 (9)	21(11)	3 (4)

\*Chi-Square test:  $p < 0.05$ .

el destinations and purposes among the 92 patients with a travel history outside Europe. The most popular travel destination was Asia/South East, and vacation was the most common travel purpose.

There was no difference in gender or age between the patients with a travel history compared to those without (Table 1). Among the 203 patients reporting a travel history outside Denmark, 139 (68%) had the biological drug administered by subcutaneous route and 43 (21%) by intravenous route, whereas 21 (11%) patients did not provide this information in the questionnaire. Among the 70 (26%) respondents, who did not report travel activities outside Denmark, the distribution of biologics was different from the group of travelers in favor of a higher prevalence of intravenously administered biologics as opposed to subcutaneously administered biologics ( $p < 0.05$  by the Chi-square test).

Compared to the travel status before versus after the initiation of biological treatment, 200 (73%) patients reported no changes in activities after initiation, whereas 42 (15%) patients reported less travel activities, and 21 (8%) patients reported more travel activities (Table 2). Moreover, 183 (67%) patients reported that neither the chronic arthritis disease nor the medical treatment had any influence on the decision to travel abroad. However, this was the case for 57 (21%) patients.

### Travel preparations

Pre-travel health advice had been sought by 52 (26%) of the 203 patients with a travel history (Table 3). Family practitioner, Internet, and the rheumatology outpatient clinic were reported as the most frequent sources for provision of pre-travel advice. However, travel medicine specialist and vaccination clinics were also consulted to some extent. One-third (35%) of the patients, who sought pre-travel health advice, did not inform the advisor about the biological treatment; among these, 72% ( $n=18$ ) stated they did not think it was important to share this information. Travel insurance coverage had been taken out by 174 (86%) patients, but only 72 (41%) of these patients had disclosed to the insurance company that they were receiving biological treatment.

### Compliance to biological treatment

Among the 139 travelers receiving subcutaneous biological treatment, 86 (62%) reported continuation of the treatment during travel, whereas 42 (30%) patients had decided to discontinue the treatment be-

**Table 2.** Patient travel activities after initiation of biological treatment.

	n (%)
After having started biologic medicine have you been:	
Travelling abroad less often than before?	42 (15)
Travelling abroad to the same extent as before?	200 (73)
Travelling abroad more often than before?	21 (8)
No answer	10 (4)
Has your rheumatic disease or medical treatment influenced your decision to travel abroad?	
Not at all	183 (67)
Yes	57 (21)
Do not know	24 (9)
No answer	9 (3)
Has your medical treatment limited your choice of travel destinations?	
Yes, I have become more cautious	66 (24)
No	207 (76)

**Table 3.** Preparation in conjunction with most recent travel abroad.

	n (%)
Among the 203 respondents with a travel history abroad:	
Were you covered by travel insurance?	
Yes	174 (86)
No	29 (14)
Among the 174 respondents covered by travel insurance:	
Did you inform the insurance company about your rheumatic disease and the biological treatment?	
Yes	72 (41)
No	102 (59)
If your treatment was changed within two months prior to travel departure, did you then make sure that the insurance coverage was still valid?	
Yes, approval was given by the insurance company	34 (20)
No change in treatment	99 (57)
No, I did not	35 (20)
No answer	6 (3)
Among the 203 respondents with a travel history abroad:	
Did you seek pre-travel advice before departing?	
Yes	52 (26)
No	151 (74)
Among the 52 respondents seeking pre-travel advice:	
Did you inform about your rheumatic disease and the biological treatment?	
Yes	34 (65)
No	18 (35)

fore travel departure owing to the concern about legal aspects of carrying the medicine on entry to another country. Logistical obstacles in handling the medicine when traveling were also reported as a reason for discontinuation. Another 11 (8%) travelers reported that they had discontinued the treatment when traveling, making a total of 53 (38%) patients pausing their subcutaneous biological treatment. Two-thirds (71%) of the 42 travelers, who stopped taking the medicine before the travel departure, did not consult their rheumatologist about this decision (Table 4).

### Health problems

A total of 13 (6%) patients reported health problems during the most recent travel. All the health problems were of minor clinical importance. Diarrhea (n=5) was the most prevalent health problem followed by aggravation/activation in rheumatology illness (n=3), fever (n=2), and other causes (n=2).

### Discussion

This questionnaire study with a response rate of 91% has shown that Danish patients with arthritis treated using biologics travel frequently to other European countries and out of Europe as well. In majority of the patients, travel activities had remained at the same level, and even increased in a proportion of them after the initiation of biological treatment. Moreover, it was also shown that patients with arthritis receiving biological treatment rarely encounter health problems when traveling, and if so, the problems are only of minor importance and not related to the chronic arthritis disease. Only 6% of patients had experienced health problems when traveling, which is in contrast to the figure of plus 50% reported in earlier studies among unselected groups of travelers (11, 12) and 19% among HIV-positive patients (3). The low prevalence among patients with chronic arthritis should be expected to some extent because the patient group may engage in more precautious resulting in less health hazardous travel activities owing to physical limitations in comparison with other groups of travelers.

The patients reported a marked tendency in discontinuation of treatment with subcutaneous biologics when traveling abroad owing to logistical challenges in transport and storage of medicine. Moreover, a concern was also reported in the questionnaire regarding carrying of medicine across the border of the destination country and anticipation of potential violation of local custom regulations. This concern

**Table 4.** Biological treatment in conjunction with most recent travel abroad.

	n (%)
<b>Among the 203 respondents with a travel history abroad:</b>	
<b>Did you continue the biological treatment as before when travelling?</b>	
Yes	86 (42)
No, stopped the treatment before travel departure	42 (21)
No, stopped during travelling	11 (5)
I was treated with infusion	43 (21)
No answer	21 (10)
<b>Among the 42 respondents who paused the treatment before travel departure:</b>	
<b>Why did you stop the treatment?</b>	
It was difficult to carry the medicine	25 (60)
I was concerned about problems with the customs authorities upon entry	9 (21)
Other reason(s)	8 (19)
<b>Did you discuss treatment discontinuation with your physician or nurse?</b>	
Yes	12 (29)
No	30 (71)

could be addressed and solved by provision of a letter to the patient from the clinic physician prior to travel departure confirming that the hand-carried medicine is approved for treatment.

It was also shown in this study that two-thirds of the patients did not seek pre-travel advice despite receiving immunocompromising treatment, which is associated with increased risk of infection. Moreover, lack of disclosure of biological treatment proved a major issue in this study, both in relation to pre-travel advice and travel insurance. It raises concern that one-third (35%) of the patients who had consulted pre-travel advisor did not disclose that they were undergoing biological treatment. It is essential for correct pre-travel advice and preparation, including travel immunization, that the advisor has the necessary knowledge about the pre-existing medical conditions, e.g., chronic arthritis requiring immunosuppressive biological treatment.

More than half of the patients with a travel insurance had not disclosed the information about the chronic arthritis disease and treatment to the insurance company. A rheumatic disease is a chronic medical condition; therefore, the patient must inform the travel insurance company in Denmark in case the treatment has been changed within the last

2 months before traveling to obtain full valid coverage in relation to the health problems occurring abroad. As a result of unstable disease activity in patients with arthritis, biological treatment is frequently adjusted by oral drugs or joint injections. Therefore, it is very important to remind the patient to inform the insurance company about any changes in the treatment in case a travel is anticipated within the next 2 months.

A limitation of this study is that the data are based on patient recall, but we believe the recall bias to have limited influence on the data.

In conclusion, Danish patients with arthritis treated using biologics travel frequently outside of Denmark. Health problems when traveling are rarely encountered and are only of minor importance. In contrast, discontinuation of biological treatment, difficulties in transport and storage of medicine, lack of pre-travel advice, and likely invalid insurance coverage are some of the major challenges, which should be addressed proactively by the staff in the patient consultation. A patient leaflet containing basic information and advice about traveling with chronic arthritis is readily available in the clinic, which could be a useful measure to raise awareness among the patients about different implications of traveling.

**Ethics Committee Approval:** This study was reported to the Danish Data Protection Agency (2008-58-0028). The regional committee of ethics did not require approval of this study.

**Informed Consent:** Written informed consent was obtained from the patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

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**Conflict of Interest:** The authors have no conflict of interest to declare.

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## References

- Conti F, Cecarelli F, Massaro L, Cipriano E, Di Franco M, Alessandri C, et al. Biological therapies in rheumatic disease. *Clin Ter* 2013; 164: e413-28.
- Dekkiche S, de Valliere S, D'Acremont V, Genton B. Travel related health risks in moderately and severely immunocompromised patients: A case-control study. *J Travel Med* 2016; 23: 1-6. [\[Crossref\]](#)
- Nielsen US, Jensen-Fangel S, Pedersen G, Lohse N, Pedersen C, Kronborg G, et al. Travelling with HIV: A cross sectional analysis of Danish HIV-infected patients. *Travel Med Infect Dis* 2014; 12: 72-8. [\[Crossref\]](#)
- Asking HH, Dalm VA. The medically immunocompromised adult traveler and pre-travel counselling: Status quo 2014. *Travel Med Infect Dis* 2014; 12: 219-28. [\[Crossref\]](#)
- Chalmers A, Scheifele D, Patterson C, Williams D, Weber J, Shuckett R, et al. Immunization of patients with rheumatoid arthritis against influenza: A study of vaccine safety and immunogenicity. *J Rheumatol* 1994; 21: 1203-6.
- Visser LG. The immunosuppressed traveler. *Infect Dis Clin North Am* 2012; 26: 609-24. [\[Crossref\]](#)
- Hall V, Johnson D, Torresi J. Travel and biologic therapy: Travel-related infection risk, vaccine response and recommendations. *J Travel Med* 2018; 25: 1-17. [\[Crossref\]](#)

8. Assen VS, Agmon-Levin N, Elkayam O, Cervera R, Doran MF, Dougados M, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic disease. *Ann Rheum Dis* 2011; 70: 414-22. [\[Crossref\]](#)
9. Shah MK. The immunocompromised traveler. *Oncology (Williston Park)* 2016; 30: 142, 145-6, 159.
10. Freedman DO, Chen LH, Kozarsky PE. Medical considerations before international travel. *N Engl J Med* 2016; 375: 247-60. [\[Crossref\]](#)
11. Steffen R, Amitirigale I, Mutsch M. Health risks among travelers-need for regular updates. *J Trav Med* 2008; 15: 145-6. [\[Crossref\]](#)
12. Hill DR. Health problems in a large cohort of Americans travelling to developing countries. *J Trav Med* 2000; 7: 259-66. [\[Crossref\]](#)