Frequency and severity of Covid-19 in patients treated with biological Disease Modifying Anti-Rheumatic Drugs (bDMARDs) for inflammatory rheumatic disease. A case-control study

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Abstract

The aim of the study was to assess the impact (frequency and severity) of Covid-19 on patients treated with biological Disease Modifying Anti-Rheumatic Drugs (bDMARDs) for inflammatory rheumatic disease and to compare it to a control group consisting of patients with musculoskeletal conditions not treated with bDMARDs.

Patients and methods:

A case control study in 200 outpatients with musculoskeletal conditions. 100 consecutive patients who have been treated with bDMARDs and 100 other consecutive patients who did not take bDMARDs were asked to complete a 15-item standardized questionnaire regarding demographic data. The following information was recorded: gender, age, weight, height, body mass index, professional activity, family status, total number of children and number of children under 18, rheumatic disease diagnosis, current treatment for rheumatism, type of containment, close contact with Covid-19 patients, Covid-19 symptoms, Covid-19 test result and hospitalization for Covid-19.

Results:

bDMARD patients mostly suffered from rheumatoid arthritis, or RA, (47%) and ankylosing spondylitis (42%). The most prescribed bDMARDs were TNF α inhibitors (57%), IL-6 blockers (12%) and JAK inhibitors (11%). The mean duration of the current biological treatment was 38.6 months. Patients from the control group were suffering chiefly from osteoarthritis (45%) and RA (21%). Compared to the control group, patients treated with bDMARDs were 10 years younger ($p < 0.001$), fewer were retired (56% versus 31%) and more were on sick or incapacity leave (6% versus 18%). During lockdown, they were more likely to be working from home or working short term (27% versus 9%). 18 patients from the bDMARDs group stopped biological treatment: one because of Covid-19 evidenced by PCR, 11 because of symptoms suggesting Covid-19 and only six from fear of contracting the disease. 12 patients, including the one Sars-CoV-2 +, resumed their treatment after a few weeks of interruption. There was no severe Covid-19 infection in the bDMARDs group. Among the three patients from the control group who had contracted Covid-19, one developed a very severe disease.

Conclusion :

This case-control study did not show an increase in the frequency or severity of Covid-19 in subjects suffering from chronic inflammatory rheumatism treated with biotherapies. Larger-scale studies are necessary before affirming that biologics do not expose patients to an increased risk of disease and complications.

Introduction

The outbreak of the coronavirus disease 2019 (Covid-19) (1) has left behind more than 500,000 global deaths among the 10 million officially diagnosed cases. Death from Sars-coV-2 virus is chiefly due to an acute respiratory distress syndrome, but also to a wide range of organ dysfunctions (2-6). In children and young adults, Covid-19 is usually mild, and not even symptomatic. On the contrary, in older and frail people, the SARS-CoV-2 virus can result in multiple organ failure, leading to death in about 4% of cases (2). Rheumatologists are on the very frontline in the management of COVID-19, although very few musculoskeletal disorders have been reported (7). The use of hydroxychloroquine for treating Covid-19, based on the antiviral activity of chloroquine (9-10) and above all that of Tocilizumab (TCZ) (11-20), a humanized anti-IL-6 receptor antibody widely used in the treatment of rheumatoid arthritis and juvenile idiopathic arthritis, has put rheumatologists in the spotlight (21, 22). Yet TCZ, like other biological Disease Modifying Anti-Rheumatic Drugs (bDMARDs), has been classified as a potentially immunosuppressive drug due to the increased risk of severe infection in patients treated with bDMARDs (23). Three questions must be raised: *i)* Is it reasonable for patients treated with bDMARDs to continue the treatment during the epidemic phase of Covid-19?; *ii)* How do we manage these patients if they are infected with SARS-CoV-2?; and *iii)* Can these patients who are 'at risk of serious infection' continue to work before an effective vaccine is available? The French Society of Rheumatology answered these issues on 21 March 2020 and sent its recommendations to all French rheumatologists. The main points to be underlined were: *i)* Persons with immunosuppression acquired by immunosuppressive therapy, biotherapy and/or corticosteroid therapy at an immunosuppressive dose may request to be put on sick leave; *ii)* If there is no sign of a Covid-19 infection, you can continue your treatment (cDMARDs, bDMARDs, corticosteroid therapy); *iii)* If there are signs of Covid-19 infection (fever, cough, shortness of breath, muscle pain), stop treatment for your rheumatism, except for corticosteroids and hydroxychloroquine. NSAIDs must be stopped; and *iv)* All patients should drastically restrict their social interactions and postpone non-emergency care. However, the preliminary reports showing the beneficial effects of a IL-6 and IL-1 blockade in Sars-CoV-2 ARDS (18, 19, 24) can paradoxically suggest a possible 'protective' effect of certain bDMARDs on Covid-19 severity. The Nord Franche-Comté hospital is located in north-eastern France, an area severely impacted by the Covid-19 outbreak (25). In our hospital, between 1 March and 30 June 2020, more than 700 patients were hospitalized for Covid-19 and 180 died. In the three neighbouring departments (Haut-Rhin, Doubs and Haute-Saône), about 4,500 patients were hospitalized and more than 1,000 died (26). The aim of the present work is to achieve an approximate estimation of the Covid-19 impact in our patients treated with bDMARDs for inflammatory rheumatic disease (IRD) and to compare it to a control group consisting of patients not treated with bDMARDs (i.e. IRD treated with cDMARDs and other musculo-skeletal conditions such as osteoarthritis, low back pain, tendinopathy etc.).

Patients And Methods

Design: Single-centre, observational cross-sectional case-control trial in 200 outpatients.

Patients: 100 consecutive patients, referred to the department of Rheumatology of the NFC hospital for an IRD, who have been treated with bDMARDs, were asked to complete a 15-item standardized questionnaire (the bDMARDs group). One hundred other consecutive patients who did not take bDMARDs

completed the same questionnaire (the control group). Before being included in the study, patients were required to give their consent to the scientific and anonymous use of the data collected in the questionnaire. The survey was achieved in compliance with the reference methodology of the French *Conseil National Informatique et Libertés* Data Protection Council (CNIL MR-001). Patients were registered under a single number, in ascending order of inclusion (neither initials nor birth dates were registered). The following information was recorded: demographic data (gender, age, weight, height, body mass index), professional activity, family status, total number of children and number of children under 18, rheumatic disease diagnosis, current treatments for rheumatism, type of containment, close contact with Covid-19 patients, Covid-19 symptoms, Covid-19 test result and hospitalization for Covid-19.

Statistics: A descriptive analysis was performed on the collected data. Qualitative variables were described using frequencies and percentages. Quantitative variables were described using mean, standard deviation and the characteristics of their distribution (minimum, maximum and median). Between-group comparisons were achieved using a student t test, chi-2 test or Fischer's exact test as appropriate. All statistical tests were carried out two-tailed at the 5% level of significance. The statistical analysis was performed using XLstats® statistical and data analysis solution (Paris, France, 2020).

Results

bDMARD patients mostly suffered from rheumatoid arthritis (47%) and ankylosing spondylitis (42%). Ten suffered from psoriatic arthritis and only one from Horton disease. Five subjects with ankylosing spondylitis (AS) had also an inflammatory bowel disease. TNF α inhibitors were the most prescribed of the bDMARDs (57%) (Table I) and the mean duration of the current biologic treatment was 38.6 months (range 1-180). Patients from the control group were suffering chiefly from osteoarthritis (45%) and RA (21%) (Table II).

The characteristics of both patient groups are summarized in table III. Patients treated with bDMARDs differed from those of the control group in age (10 years younger; $p < 0.001$) and the number of children under 18 (2 times less; $p = 0.02$). As expected, they were also more likely to be retired (56% versus 31%) and less likely to be on sick or incapacity leave (6% versus 18%). However, those who were still working during the lockdown were more likely to have jobs requiring direct contact with the public or patients (13% versus 4%). On the other hand, bDMARD patients were more likely to be working from home or working for only a short period of time (27% versus 9%). Patients treated with bDMARDs have been less frequently in contact with Covid-19 patients, but the difference did not reach statistical significance ($p = 0.16$).

18 patients from the bDMARDs group stopped their biological treatment. Among them, only one stopped bDMARDs (Adalimumab) because of Covid-19 evidenced by PCR, 11 because of mild to moderate symptoms that suggested an infection and six asymptomatic subjects stopped treatment due to fear of contracting the disease. However, 12 patients, including the one Sars-CoV-2 +, resumed their treatment after a few weeks of interruption. There was no severe Covid-19 infection in the bDMARDs group. Among the three patients from the control group who had contracted Covid-19, a 72-year-old woman with

osteoarthritis developed a very severe disease with ARDS, that required her to be admitted into the intensive care unit for mechanical ventilation. She recovered totally within two months.

Discussion

The first lesson we can learn from this study is that most patients treated with biologics continued treatment in accordance with the recommendations of the French Society of Rheumatology. Only 6% interrupted treatment for fear of the disease. The other patients who had to stop their biological treatment did so when they developed symptoms compatible with the Sars-Cov-2 infection, and all of the patients resumed treatment after the symptoms had disappeared or once the PCR had been shown to be negative.

It is difficult to assert that patients with biologics are no more at risk of Covid-19 than control patients, since the number of infected subjects was very low in the two groups. However, our results suggest that taking a biologic is not a risk factor for contracting the disease. The only Covid-19 positive case was mild, unlike the control group where a patient, without significant risk factors except her age (72 years) developed a severe form requiring admission into the ICU.

However, it is possible that patients treated with biologics took more precaution during containment and that they were less in contact with sick subjects. Although they were more frequently in close contact with children under the age of 18, they were on sick leave or working from home more often than the control subjects.

In conclusion, this case-control study, carried out in a region very strongly impacted by Covid-19, did not show an increase in the frequency or severity of the infection in subjects suffering from chronic inflammatory rheumatism treated with biotherapies.

Larger-scale studies, carried out outside a containment period, are necessary before affirming that biologics do not expose patients to an increased risk of disease and complications.

Declarations

Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Ethics declarations

Conflict of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Due to the retrospective nature of the study, the Ethics Committee determined that only oral patient consent was required.

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None

Availability of data and materials

All data generated or analysed during this study are available at the Unité de Recherche Clinique, Hôpital Nord Franche-Comté, Belfort, France.

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Tables

Table I: List of the Biological Disease Modifying Anti-Rheumatic Drugs (bDMARDs group)

bDMARDs	Number of patients
ABATACEPT	4
ADALIMUMAB	19
BARICITINIB	7
CERTOLIZUMAB	1
ETANERCEPT	15
GOLIMUMAB	13
INFLIXIMAB	9
IXEKIZUMAB	1
RITUXIMAB	4
SARILUMAB	1
SECUKINUMAB	7
TOCILIZUMAB	11
TOFACITINIB	4
USTEKINUMAB	4

Table II: Rheumatic diseases in the control group

Rheumatic diseases	Number of subjects
Osteoarthritis	45
Rheumatoid arthritis	21
Polymyalgia rheumatic/ Horton disease	7
Ankylosing spondylitis	6
Tendinopathy	6
Fibromyalgia	3
Chondrocalcinosis	3
Sciatica	3
Systemic lupus erythematosus	2
Others (meniscopathy, villonodular synovitis, SAPHO syndrome, Infectious spondylodiscitis)	4

Table III: Characteristics of patients treated with Biological Disease Modifying Anti- Rheumatic Drugs (bDMARDs) or not (Controls)

Variables	All	bDMARDs	Controls	P-values
Age (years) Mean (range)	59 (23-89)	54 (25-81)	64 (23-89)	<0.001
Weight (kg) Mean (range)	75.3 (41-145)	75.7 (45-121)	74.5 (41-145)	0.64
Height (cm) Mean (range)	166.4 (140-195)	166.4 (148-187)	165.8 (140-195)	0.62
Body Mass Index Mean (range)	27.2 (16.8-48.1)	27.3 (17.9-48.1)	27.0 (16.8-44.9)	0.74
Sex ratio (F/M)	127/93	62/48	65/45	0.66
Nb children Mean (range)	1.71 (0-5)	1.7 (0-5)	1.78 (0-4)	0.87
Nb of children<18 Mean (range)	0.54 (0-5)	0.7 (0-5)	0.36 (0-3)	0.02
Life in couple/alone (N)	156/44	80/20	76/24	0.69
Retired (%)	87	31	56	0.001
Sick or incapacity leave (%)	48	31	17	0.02
Working from home/short-term working (%)	36	27	9	<0.0001
Work with public or patients (%)	17	4	13	0.01
Methotrexate or leflunomide (%)	47	29	18	0.04
Corticosteroid (%)	13	7	6	0.90
Covid-19 symptoms (yes/no)	27/173	12/88	15/85	0.45
PCR assessment (%)	11	4	7	0.55
PCR+ (%)	4	1	3	0.84
Contact with Covid-19 subject (yes/no/uncertain)	27/156/18	10/84/6	17/72/11	0.16
Stop bioM (yes/no)	18/182	18/82	NA	NA