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Use of biologic agents in idiopathic inflammatory myopathies in Sweden: a descriptive study of real life treatment

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ABSTRACT

Objective. *Biologic treatment has revolutionised treatment in rheumatology in the last decades. Patients with idiopathic inflammatory myopathies (IIM) have so far only been treated with biologics off-label, with little published follow-up on those who are treated and how they are treated. We therefore set out to characterise the Swedish IIM patients who have been treated with biologics.*

Methods. *By linking Swedish registers we identified 95 patients with IIM who were treated with biologics between 2000 and 2011. Via chart review the diagnoses were validated and clinical characteristics extracted.*

Results. *In total, 95 individuals with IIM and biologic treatment were identified. Median disease duration was 5.5 years at start of biologics. All patients had been treated with prednisolone and failed at least one previous DMARD before the start of first biologic. Rituximab was the most common biologic drug, followed by anakinra and TNF-inhibitors. Median overall treatment length was 10 months and varied between 5 and 12.5 months or the different therapies.*

Conclusion. *Off-label treatment of IIMs is often tried and seldom successful. This study shows a large unmet need for novel treatments and therapies in IIM. It is therefore important to follow these patients in a structured way to learn about effects and potential risks for different subgroups of IIM associated with different therapies.*

Introduction

Idiopathic inflammatory myopathies (IIM) are chronic inflammatory diseases, mainly affecting skeletal muscles. They are traditionally divided into four major subsets, polymyositis (PM), dermatomyositis (DM), juvenile DM (JDM), affecting children under 18 years, and sporadic inclusion body myositis (IBM) (1). IIM are treated with high doses of glucocorticoids as first line therapy and addition of immunosuppressants such as methotrexate or azathioprine is common (2). However, many patients have a limited response or experience side effects to treatment (3).

Biologic agents have changed the life for patients with several other autoimmune diseases, *e.g.* rheumatoid arthritis (RA), and they have also been used off-label to treat refractory IIM. Multiple reports based on case reports and open label clinical trials have been published regarding the effectiveness of different biologics agents in IIM, sometimes with contradicting results (4-7) while the only placebo-controlled trial using biologics in IIM published so far, the Rituximab in Myositis (RIM)-trial, failed to meet the primary end-point, time to meet the DOI, even though 83% of patients met the definition of improvement (DOI) after 8 weeks, (8). Much is still unknown about how biologics have been used to treat IIM-patients. Therefore the aims of this study were to:

- Identify all IIM-patients in Sweden ever treated with biologics using national patient registers
- Describe this unselected cohort of patients in terms of clinical characteristics
- Assess treatment length and reasons for stopping treatment

Materials and methods

In Sweden, IIM-patients are treated by rheumatologists, dermatologists, neurologists and internal medicine speciliasts, while juvenile cases are treated by pediatricians. There is universal access to publicly funded health care for all residents.

Study population

To identify all IIM-patients in Sweden treated with biologics between 2000 and 2011 we linked the following registers:

The Swedish Rheumatology Quality of care Register (SRQ) is an online register used in clinical practices in Swedish rheumatology clinics listing information on diagnosis, treatment and disease activity variables. SRQ includes 87% of all RA patients treated with biologics (9).

The Swedish Patient Register lists all in-patient visits, with national coverage from 1987, and out-patient hospital visits from 2001, in Sweden. IIM-patients were identified using International Classification of Diseases (ICD) 9 and 10 codes (Fig. 1).

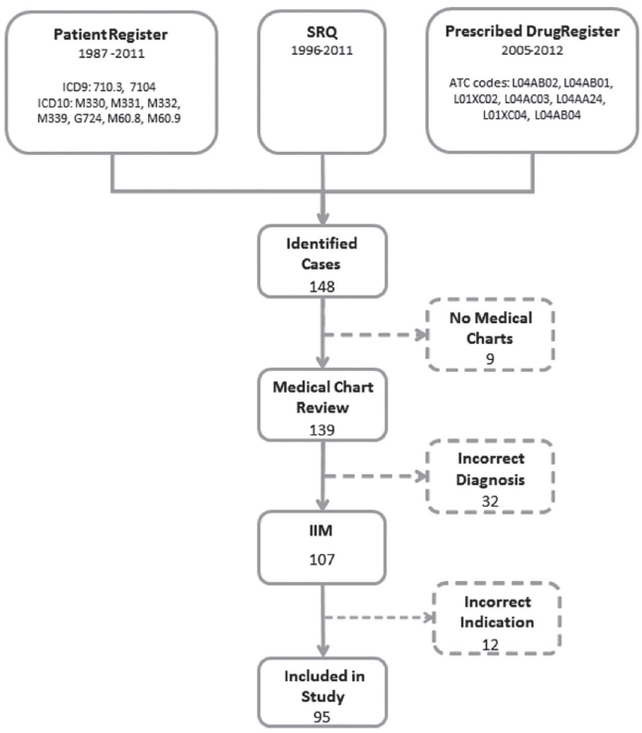

Fig. 1. Flow chart describing exlusion and inclusion of patients identified from the specified registers. International classification of disease (ICD) codes, version 9 and 10, were used to identify patients from the patient register. Anatomical therapeutic chemical (ATC) classification system was used to identify biologic treatments from the prescribed drug register. Incorrect diagnosis included Juvenile idiopathic arthritis, juvenile polyarthritis, juvenile rheumatic arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis.
SRQ: Swedish Rheumatology Quality Register; IIM: idiopathic inflammatory myopathies.

The Swedish Prescribed Drugs Register contains data on all drugs dispensed from pharmacies in Sweden from July 2005 and onward with complete coverage for filled prescriptions in ambulatory care. This register was used to identify pharmacy-dispensed biologics using Anatomical Therapeutic Chemical Classification (ATC)-codes (Fig. 1). Medical charts were reviewed to confirm IIM-diagnosis and indication for biologic treatment. For inclusion in the study, the patient had to be diagnosed with an IIM-diagnosis by treating physician.

Outcomes and variable description

Variables used to describe the population included diagnosis, demographic data, disease duration and disease activity variables included in the core set measurements suggested by the International Myositis Assessment and Clinical Studies group (IMACS) (10). IMACS variables were collected at start of treatment from SRQ and medical charts.

Treatment length was collected from medical records. Reason for stopping treatment was assessed within two years from starting biologic treatment. Drug discontinuation was defined as: (1) drug stopped by treating physician, (2) start of another treatment where combination of therapies was not explicitly expressed. If these criterion were not met; date for drug discontinuation was set to date of last given dose +6 months for rituximab, +1 month for abatacept and infliximab and +0.5 months for adalimumab and anakinra. Information on patient characteristics and treatment was described at start of first biologic treatment for all patients.

This study was approved by the Regional Ethics Committee at Karolinska Institutet, Stockholm.

Results

Study population

One hundred forty-eight patients were identified from the patient register and SRQ. After review of medical records, 95 patients had confirmed IIM diagnosis and correct indication and were included in the study (Fig. 1). Patients were identified from 16 different hospitals all over Sweden.

Patient characteristics

Median disease duration at start of first biologic was 5.5 years. All patients had been treated with prednisolone and had failed at least one previous disease modifying anti-rheumatic drug (DMARD) before start of first biologic (Table I). Methotrexate and azathioprine were the most commonly used DMARDs (68% and 44%, respectively). Availability of data on the different IMACS disease activity core set variables (Table I) ranged between 46-50% at start of treatment.

Patients started on biologic treatment had a severe muscle weakness with a median manual muscle test (MMT)-8 of 58/80 and with a functional impairment suggested by the elevated HAQ score. The overall disease activity was rated medium by the physician but high by patients (Table I).

Biological treatment was given with concomitant DMARDs and prednisolone in 73% and 70% of cases respectively (Table II). Rituximab was the most commonly used biologic agent to treat IIM followed by anakinra and TNF-inhibitors. Median overall treatment length was 10 months and varied between 5 and 12.5 months for the different therapies. The most common reason for stopping treatment was *no effect* followed by *adverse event* (Table II).

One hundred and thirty-six biological treatments were started during the study period. More than one biologic agent was prescribed to 27 patients (28%). No difference was seen in age, gender or clinical sub-diagnosis between patients receiving only one biologic agent compared to patients receiving multiple agents.

The most common switch for patients treated with TNF-inhibitors was to anakinra (n=10, 56%) or rituximab (n=5, 28%) while rituximab failures were most commonly switched to abatacept (n=3, 50%) and anakinra failures were followed by rituximab or abatacept (both n=2, 40%).

A shift of drugs used during the study period was observed as well as an overall increased usage of biologics over time (Supplementary Fig. 1).

Discussion

In this population-based study, the combination of multiple national registers enabled us to identify 95 IIM-patients who had been treated with at least one biologic agent in Sweden between 2000 and 2011. Biologics were given to treatment-resistant patients with per-

Table I. Clinical characteristics and disease activity variables at start of treatment with first biologic agents of 95 patients with idiopathic inflammatory myopathies identified between 2000 and 2011.

Diagnosis	Overall	Polymyositis	Dermatomyositis	Juvenile dermatomyositis	Inclusion body myositis
n	95	31	27	8	29
Women, n (%)	56 (59%)	24 (77%)	16 (59%)	6 (75%)	10 (34%)
Age, median (p25-p75)	57 (48-67)	59 (52-65)	53 (48-58)	15.5 (12-23)	67 (60-74)
Jo-1, n (%)	17 (18%)	8 (26%)	9 (33%)	0 (0%)	0 (0%)
Disease duration (years), median (p25-p75)	5.5 (3-11)	7.5 (4-13)	4 (2-8)	3 (2-14)	5 (3-11)
IMACS core set measures, median (p25-p75)					
Physician disease activity, VAS (0-100)	30 (20-50)	33.5 (17-52)	50 (30-50)	*	25 (15-30)
Patient disease activity, VAS (0-100)	64.5 (48-77)	70 (63-79)	72 (58-82)	*	54 (33-67)
MMT8	58 (52-66)	64.5 (56-74)	61 (51-72)	57 (57-57)	54 (48-62)
Extra muscular disease activity, VAS (0-100)	10 (0-30)	10 (9-18)	40 (33-50)	*	0 (0-6)
HAQ	1.55 (1-2)	1.45 (1-2)	0.9 (1-1)	*	1.85 (2-2)
CK x ULN	1.2 (0-3)	1.2 (0-4)	1.4 (0-4)	3.1 (2-3)	1.2 (1-2)
LD x ULN	1.5 (1-2)	1.7 (2-2)	1.35 (1-3)	1.2 (1-1)	1.4 (1-2)
Diagnosis of IIM**					
Definite	24 (25%)	11 (35%)	10 (37%)	3 (38%)	0 (0%)[¥]
Probable	20 (21%)	9 (29%)	8 (30%)	3 (38%)	-
Possible	16 (17%)	0 (0%)	1 (4%)	0 (0%)	15 (52%)
Missing detailed information	35 (37%)	11 (35%)	8 (30%)	2 (25%)	14 (48%)
Previous medication					
Steroids, n (%)	92 (97%)	29 (94%)	26 (96%)	8 (100%)	29 (100%)
n DMARDs, mean (sd)	2.3 (1.2)	2.4 (1.3)	2.7 (1.3)	1.9 (0.8)	1.8 (1.1)
Methotrexate	65 (68%)	16 (52%)	19 (70%)	7 (88%)	23 (79%)
Azathioprine	42 (44%)	15 (48%)	15 (56%)	1 (12%)	11 (38%)
Mycophenolate mofetile	14 (15%)	7 (23%)	5 (19%)	1 (12%)	1 (3%)
Cyclophosphamide	20 (21%)	11 (35%)	8 (30%)	0 (0%)	1 (3%)
Cyclosporine	28 (29%)	10 (32%)	14 (52%)	1 (12%)	3 (10%)
Tacrolimus	4 (4%)	1 (3%)	1 (4%)	2 (25%)	0 (0%)
IVIG	28 (29%)	8 (26%)	8 (30%)	3 (38%)	9 (31%)

*No data available. **Bohan and Peter criteria (13, 14) for polymyositis, dermatomyositis and juvenile dermatomyositis. Griggs criteria (15) for inclusion body myositis. ***Insufficient information on muscle biopsies to fulfill all criteria required according to the Griggs diagnostic criteria (15). IIM: idiopathic inflammatory myopathies; IMACS: International Myositis Assessment and Clinical Studies group; VAS: visual analogue scale (1-100); MMT8: manual muscle test (0-80); HAQ: Health Assessment Questionnaire (0-3); CK: creatine phosphokinase; LD: lactate dehydrogenase; ULN: upper limit of normal; DMARD: disease-modifying anti-inflammatory drugs; IVIG: intravenous immunoglobulin.

sisting severe muscle weakness after having tested at least one conventional immunosuppressive drug and were usually given in combination with another DMARD and prednisolone.

An overall increased use of biologics during the past years was observed which might be explained by the availability of new agents approved for rheumatic disorders over time and an increasing number of published case reports on the experience of biologics in IIM. It may also suggest an unmet need for new therapies in IIM.

Patients treated with anakinra were most prone to stop treatment due to adverse events; it was reported more often than for RA-patients (11) while the frequency of IIM-patients stopping TNF inhibitors was similar to what has been reported in RA (12). There were some variations in treatment length for the different IIM subgroups but because of the small numbers, as well as differences in baseline characteristics and dose intervals, it is difficult to make any conclusions regarding differences in treatment length.

We believe that we have captured most IIM-patients who were treated with biologics in Sweden due to the complete coverage of patients treated with biologics in the SRQ register for all rheumatology diagnoses. Still, we may have missed some patients as the prescribed drug register was not available for the whole study period. Furthermore, intravenous drugs administrated in the hospital are not captured by the prescribed drug register but these could still be identified through the SRQ register.

The diagnoses of included patients were confirmed using medical charts. Due to missing information on some variables, especially muscle biopsy features and EMG reports, it was difficult to use diagnostic or classification criteria (13-15) to confirm IIM diagnosis. Another limitation is that we had disease activity measures according to IMACS criteria on only half of the patients, thus we could not assess the effect of biological treatment on disease activity.

With this study we aimed to investigate real life use and treatment length of biologics in IIM patients in Sweden. Biologic therapies are frequently used to treat IIM off-label and it is important that these patients are followed in a structured way, *i.e.* in registers like SRQ, to give us a better understanding as to which therapies may be effective in which subgroups of patients. It is also important to enhance the understanding of the influence of different molecular pathways important in IIM

Table II. Treatment length, reason for stopping and concomitant treatment at start of first biologic treatment for patients with idiopathic inflammatory myopathies.

Biologic agent	Overall	Rituximab	TNF-inhibitors	Anakinra	Abatacept
n	95	39	27	25	4
Diagnosis					
PM	31 (33%)	17 (44%)	8 (30%)	5 (20%)	1 (25%)
DM	27 (28%)	19 (49%)	3 (11%)	3 (12%)	2 (50%)
JDM	8 (8%)	1 (3%)	6 (22%)	1 (4%)	0 (0%)
IBM	29 (31%)	2 (5%)	10 (37%)	16 (64%)	1 (25%)
Treatment length (months)					
mean (sd)	19 (21)	24 (25)	14 (18)	17 (20)	20 (23)
median (p25-p75)	10 (4-27)	12 (6-38)	5 (3-19)	9 (4-20)	12.5 (5-28)
Reason for stopping*					
Adverse event	22 (23%)	5 (13%)	8 (30%)	9 (36%)	0 (0%)
No effect	34 (36%)	13 (33%)	12 (44%)	8 (32%)	1 (25%)
Planned	2 (2%)	1 (3%)	0 (0%)	1 (4%)	0 (0%)
Remission	4 (4%)	3 (8%)	1 (4%)	0 (0%)	0 (0%)
Death	1 (1%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
Other	3 (3%)	2 (5%)	1 (4%)	0 (0%)	0 (0%)
Unknown	8 (8%)	2 (5%)	4 (15%)	1 (4%)	1 (25%)
Concomitant treatment					
On prednisolone	59 (70%)	28 (80%)	12 (60%)	15 (60%)	4 (100%)
Prednisolone (mg/d), median (p25-p75)	10 (8-15)	13.5 (10-20)	11.5 (7-13)	8 (6-8)	8 (7-10)
On DMARDs	61 (73%)	25 (71%)	15 (75%)	18 (72%)	3 (75%)
Methotrexate	38 (40%)	12 (31%)	13 (48%)	11 (44%)	2 (50%)
Azathioprine	10 (11%)	3 (8%)	2 (7%)	5 (20%)	0 (0%)
Mycophenolate mofetile	5 (5%)	4 (10%)	0 (0%)	1 (4%)	0 (0%)
Cyclophosphamide	3 (3%)	1 (3%)	0 (0%)	1 (4%)	1 (25%)
Cyclosporine	3 (3%)	3 (8%)	0 (0%)	0 (0%)	0 (0%)
Tacrolimus	2 (2%)	2 (5%)	0 (0%)	0 (0%)	0 (0%)

*Of started treatments that stopped within 2 years or at last follow-up (74 (78%) treatments were stopped within 2 years). Values are *n (%)* unless otherwise indicated. End of treatment defined as treatment cessation or end of study period. TNF-inhibitors: etanercept, adalimumab, infliximab; PM: polymyositis; DM: dermatomyositis; JDM: juvenile dermatomyositis; IBM: inclusion body myositis; DMARD: disease-modifying anti-inflammatory drugs.

treatment, so that this patient group will have greater treatment options available in the future.

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