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## **Adalimumab and myositis: a case report and review of the French and international Pharmacovigilance databases**

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## **Abstract**

TNF $\alpha$  inhibitors, including adalimumab, are widely used in inflammatory rheumatologic and bowel diseases. Well-known adverse effects include: opportunistic infections, immunogenicity and new inflammatory manifestations. Myositis is an inflammatory disease which expresses with muscle symptoms and can be life-threatening. A few is known about drug-induced myositis. We aimed to describe a case of myositis induced by adalimumab and reviewed national and international pharmacovigilance databases for other cases until 01/02/2019. This was a 63 years old woman with Crohn's disease, who developed muscle weakness and rhabdomyolysis 3 months after starting adalimumab. Diagnosis of myositis was suspected and confirmed with electromyography and muscle biopsy. Improvement in muscle symptoms was observed after stopping adalimumab and starting corticosteroids. Muscular adverse effects are well-known and usually benign with adalimumab. However, five cases of myositis during treatment with adalimumab were registered in French Pharmacovigilance Database (FPVD) with muscle symptoms observed 3 months to 7 years after starting adalimumab. In VigiBase<sup>®</sup>, 90 cases of myositis associated with adalimumab with some similar characteristics were registered. When a patient treated with adalimumab complains of muscular symptoms, inflammatory myopathies should be considered. This adverse effect should be mentioned in Summary of Product Characteristics to alert healthcare professionals.

## **Introduction**

Since the early 2000s, TNF $\alpha$  inhibitors have revolutionized the treatment of inflammatory rheumatologic disease and chronic inflammatory bowel disease such as Crohn's disease [1,2]. TNF $\alpha$  is a pro-inflammatory cytokine with multiple pleiotropic effects including apoptosis, cellular proliferation and pro-inflammatory cytokines production [3]. It has been implicated in various auto-immune diseases. Anti-TNF $\alpha$  therapies have demonstrated their consistent and remarkable efficacy in controlling signs and symptoms, with a favorable safety profile [4]. Their main adverse effects are opportunistic infections related to immunosuppression, lymphomas, congestive heart failure, injection site reactions, and immunogenicity [5–7]. Moreover, TNF $\alpha$  inhibitors have been associated with treatment resistance in auto-immune disease [8] or even to the appearance of new inflammatory manifestations such as demyelinating disease [9] or lupus-like syndrom [10]. The origin of this induced- immunogenicity remains unclear, but might be secondary to cytokine imbalance [11].

Myositis is an inflammation of the skeletal muscle tissue, which can manifest as muscle weakness, or myalgia and can lead to potentially life-threatening conditions such as deglutition disorders or respiratory failure. Subgroups of myositis have been described, as for instance dermatomyositis, sporadic inclusion body myositis, immune-mediated necrotizing myopathy and overlap myositis (this former including among others anti-synthetase syndromes and other inflammatory myopathies designed as polymyositis) [12,13]. Diagnosis remains on muscle weakness (often proximal in the limbs) eventually with associated organ disease (skin, interstitial pneumonia, arthritis...), elevated serum CK levels, presence of myositis specific antibodies (except for inclusion body myositis) and may be associated in some cases with muscle biopsy features suggestive of inflammation such as infiltration of mononuclear cells, myonecrosis or diffuse HLA-1 expression [14]. Except for inclusion body myositis, treatment relies on corticosteroids and eventually immunosuppressant drugs [15].

Several drugs have been associated with myositis, this Adverse Drug reaction (ADR) being mentioned in Summary of Product Characteristics (SmPC) of: some protease inhibitors (amprenavir, darunavir, fosamprenavir, indinavir, ritonavir, nelfinavir, saquinavir and

tipranavir), daptomycine, phenytoin, or in literature (tretinoin [16–19], interferon- $\alpha$  [20-21], statins and fibrates [22] and more recently immune checkpoint inhibitors [23]). Nevertheless, frequency of drug-induced myositis needs to be quantified.

We aimed to describe a case of adalimumab-induced myositis and other cases registered in the French Pharmacovigilance Database (FPVD) and in VigiBase<sup>®</sup> (the WHO global database of individual case safety reports (ICSRs)).

## **Methods**

We first report a case of myositis induced by adalimumab, then make a review of the cases registered in the French Pharmacovigilance Database (FPVD). FPVD gathers all consecutive ADR reported by every healthcare professionals (hospitals and liberals) and patients in France, and collected by the 31 French regional pharmacovigilance centers since 1985 (each center recording ADR from its territory). Every reported ADR was analyzed by a local college of pharmacologists. ADR were encoded by using the MedDRA (Medical Dictionary for Regulatory Activities, version 22.1) classification. Here, we used the High Level Term (HLT) “Muscles infections and inflammations” and request was done on 02/01/2019. For each ADR, we used demography data (sex, age), medical history, clinical manifestations, delay of onset, electromyography findings, immunologic lab tests, histopathology of muscular biopsy, possible differential diagnosis, medical care (especially if adalimumab was stopped) and outcome. If some of these informations were missing, we asked the regional pharmacovigilance center to fill up. Cases were excluded if histopathological and complementary tests to confirm the diagnosis of myositis were not available.

To evaluate the individual causal relationship between adalimumab and myositis we used the Naranjo adverse drug probability scale [24]. The Naranjo scale ranges from -4 to +13 and the drug reaction was considered definite if the score was  $\geq 9$ , probable if between 5 to 8, possible if between 1 to 4, and doubtful if  $\leq 0$ . This scale relies on 10 criteria including: chronological criteria (for example: symptoms started after the suspected drug was administered, improvement was observed after stopping it), semiological criteria (for example: other etiologies have been excluded) and bibliographical data (previous description of similar adverse effect with this drug).

Then, we used VigiBase<sup>®</sup>. Drugs recorded have been coded according to WHODrug to specify the drugs and MedDRA (version 22.1) to specify the adverse effects. Request used 2 Preferred Term (PT): “myositis” and “polymyositis” and adalimumab as a substance, and was done until 02/01/2019.

## **Results**

### *Case report*

A 63-year-old woman was referred to the internal medicine department for sub-acute weakness and rhabdomyolysis. Her medical history included Crohn’s disease for 5 years, benign pancreatic tumour (intraductal papillary mucinous neoplasm), type 2 diabetes, hypertriglyceridemia, active smoking, cholecystectomy for lithiasis, acute hepatitis A and a cholestatic hepatitis which was considered to be related to ciprofloxacin or pregabalin, or to a primary sclerosing cholangitis. There was no notable familial history. She was treated with adalimumab since 8 months for Crohn’s disease and with ursodeoxycholic acid, gliclazide and saxagliptin for few years. She received no other treatment, especially no lipid-lowering drug. Since the beginning of adalimumab at 40 mg every two weeks, she complained of slight weakness in her four limbs. Two months before admission, adalimumab was increased to 40 mg every week because of an insufficient control of Crohn’s disease. This dose enhancement was associated with a dramatic increase of limb weakness, dysphagia and hands joints pain predominating in the morning. Upon admission, physical examination revealed a four-limb weakness predominating in proximal muscles, difficulties getting out of a chair, and quadricipital amyotrophy. There was no skin lesion evocative of dermatomyositis, no mechanic’s hands and no evidence of pulmonary or vascular involvement. Lab tests revealed an elevation of creatine kinase (CK) levels up to 866 U/L (normal: 20-180 UI/L), and chronic inflammatory syndrome (C-reactive protein at 20 mg/l, fibrinogen at 5.1 g/l). Electromyography (EMG) confirmed myogenic involvement with abnormal spontaneous activities in the biceps, tibialis anterior and vastus medialis muscles. Quadriceps biopsy was consistent with myositis with a lymphocytic infiltrate in the endomysium (80-90% of T-cells), invasion of non-necrotic fibres, myonecrosis, ragged red fibres, 20% of Cytochrome C-negative fibres, diffuse HLA-1 expression and diffuse C5b-9 reactivity of sarcolemma and few capillaries. There was no rimmed vacuole, but p62 and TDP43 staining revealed few inclusions. Immunologic tests revealed positive anti-nuclear

antibody on Hep-2 cells (1/640), rheumatoid factors (58 UI/ml), IgG anti-cardiolipin antibodies (10 U/ml) and anti-beta-2 glycoprotein 1 antibodies (16 U/ml). There was no specific-myositis antibody, no anti-extractable nuclear antigens antibody, no anti-native DNA antibody, no anti-cyclic citrullinated peptide antibody. Viral serologies (HIV, HVC, HVE, CMV, human parvovirus B19, HSV, EBV, enterovirus) were all negatives. Thoracic CT-scan and echocardiography were normal. Clinical examination, positron emission tomography, mammography and pelvic sonography did not showed evidence of a neoplasm. Considering the delay of onset (symptoms beginning immediately after adalimumab introduction and aggravated with dose enhancement), drug involvement was suspected, adalimumab was stopped, which allowed a moderate but immediate improvement of symptoms. Prednisone 1 mg/kg was then introduced, leading to a complete regression of symptoms in 4 months and a normalisation of CK levels (28 UI/l) and of the EMG. Because of recurrence of Crohn's disease, vedolizumab was started. During the following 12 months, no muscle symptom was observed for this patient.

#### *Review of the French Pharmacovigilance Database*

In addition to our case, we retrieved seven cases of inflammatory myopathies related to adalimumab registered in the FPVD, from various cities in France. Two cases were excluded because of lacking data, thus we collected data from five other cases from the FPVD (Table 1). Among these 5 cases of myositis, 4 occurred in women. Patients were aged 36 to 61 years old and treated with adalimumab for various disorders (one case each): ankylosing spondylitis, rheumatoid arthritis, psoriasis, Crohn's disease, and chronic inflammatory bowel disease associated with ankylosing spondyloarthritis. First symptoms were myalgia and/or muscle weakness and occurred 3 months to 7 years after starting adalimumab and adalimumab was the only treatment suspected in 4 cases. Increased CK levels were observed in all cases. Histopathological aspect of myositis was confirmed in muscle biopsy in all cases. Common features were an irregular diameter of muscle fibers, myonecrosis, endomysial infiltration by mononuclear cells and diffuse HLA1 expression. Conversely, some features were isolated: one subject (case n°1) displayed ragged red fibers, COX negative fibers and rare p62-positive inclusions, one subject (case n°6) presented rimmed vacuoles and rare granulomatous formations, for whom sarcoidosis was not



excluded. Electromyograms were performed in all cases and found myogenic patterns in 4 cases and remain normal in the other cases. Auto-antibodies, especially antinuclear antibodies (which can be induced by TNF-alpha), were present in 4/5 but none showed myositis specific antibodies. Other causes of myositis, especially paraneoplastic and/or viral, were ruled out in most (4/5). The pharmacological investigation included a complete history of treatments intake for each case, and all the imputability of all the treatments was studied. Only one patient (case n°5) had two other treatments which could be suspected to be involved in the myositis: infliximab (TNF $\alpha$  inhibitor) which was stopped before the onset of myositis and was switched for adalimumab, and methotrexate prescribed 5 months earlier and pursued concomitantly to adalimumab. Both treatments were prescribed for the inflammatory bowel disease and/or the ankylosing spondylitis. For this patient, the temporal profile was in favor of imputability of adalimumab rather than of the two other treatments. Stopping adalimumab and/or introducing a treatment with corticosteroids and/or immunosuppressant drugs allowed improvement in 2 cases and stabilization in 2 cases. Causality assessment, according to Naranjo's scale showed a probable relationship between adalimumab and myositis in 1 case and a possible relationship in the 4 others cases. It is interesting to note that the last patient (n°6) experienced myalgia when he tried adalimumab 2 years before. The early discontinuation of adalimumab led to improvement of symptoms.

#### *Review of VigiBase®*

Among the 430 829 reports with adalimumab until 02/01/2019, 28 cases of polymyositis and 79 cases of myositis have been recorded. After excluding cases already registered in FPVD, published in literature or associated to another auto-immune or auto-inflammatory manifestation, we retained 68 and 22 cases respectively. Adalimumab was the only drug suspected in a large majority (90 %) and mainly prescribed in rheumatoid diseases and also inflammatory bowel disease or psoriasis. Time to onset ranges from 14 days to 8 years (median time to onset = 7.5 months) after starting adalimumab (among 28 known data). Outcome was favorable after stopping TNF $\alpha$  inhibitor in 21 cases (and unknown in the others cases) but information about specific treatment was not available.

## Discussion

We describe 6 cases of myositis induced by adalimumab from the French Pharmacovigilance Database, with a majority of female patients and occurring after a few months to a few years of treatment. Muscular adverse reactions are reported with adalimumab and mentioned in SmPC, including very frequent musculoskeletal pain, frequent muscle spasms and infrequent rhabdomyolysis. However, inflammatory myopathies (collectively known as myositis) seem to be rarer. Only exacerbated symptoms of a subtype of myositis (dermatomyositis) is specified in SmPC for adalimumab. This is also mentioned for some other TNF $\alpha$  inhibitors (etanercept, infliximab and certolizumab).

Data from VigiBase<sup>®</sup> strengthen this case-series, and may suggest a causal relationship between adalimumab treatment and onset of myositis. Nevertheless, it is important to keep in mind that the information comes from a variety of sources, details about biological, clinical and histological data were lacking, so the probability that the suspected adverse effect is drug-related is not the same in all cases. Moreover, because details about these cases were not available, we cannot exclude a protopathic bias because some disease treated with adalimumab (such as Crohn disease) can also cause myositis-like complications (25,26). Nevertheless it is almost impossible to rule out a myositis-like complication of the initial disease as they can be unrelated to usual manifestations of this disease; for instance extra-digestive manifestations of Crohn's disease can occur as there is no digestive activity of the disease and thus no digestive signs.

Six cases of myositis induced by adalimumab have already been identified in a literature review by *Zengin et al.* in 2017 among 24 patients treated with various TNF $\alpha$  inhibitors, suggesting a class effect [27]. Interestingly, characteristics of these cases are similar to our cases. Patient were majority female (14/24 patients). TNF $\alpha$  inhibitors were used to treat various diseases but mostly rheumatic diseases. Times to onset were rather long, between 2 months to 3 years after starting TNF $\alpha$  inhibitors (excluding 2 patients successively treated with 2 TNF $\alpha$  inhibitors: adalimumab for 2 weeks and then infliximab for 1 month in the first case and etanercept for 10 years and then adalimumab for 2 weeks in the second case). Improvement (complete or partial) was observed in most cases after stopping TNF $\alpha$  inhibitor (except for 2 partial responses) and with corticosteroids or immunosuppressant treatment. To note, treatment with corticosteroids can allow a

favourable outcome despite continuing etanercept in some cases [28]. Results of muscular biopsy were not detailed. Specific myositis antibody (anti-Jo1) were not consistently present (7/24 cases). Among other TNF $\alpha$  inhibitors, etanercept was mostly involved (11 cases) followed by infliximab (6 cases). Considering these cases, we can hypothesize that there is a “pattern” for TNF $\alpha$  inhibitors induced myositis: subacute myositis without extra-muscular involvement (especially no skin lesion), no myositis specific antibodies observed, no evidence of viral infection or neoplasm, and symptoms resolution when the anti-TNF therapy was stopped, associated with immunosuppressant drugs and/or corticosteroids. This pattern does not always match with classical idiopathic myositis subtypes (dermatomyositis, sporadic inclusion body myositis, immune-mediated necrotizing myopathy, antisynthetase syndrome).

It is well known that TNF $\alpha$  inhibitors can induce paradoxical autoimmune disorders such as: vasculitis, hepatitis, lupus-like syndrome, interstitial lung diseases, uveitis [29], and also sarcoidosis [30]. Inflammatory myopathies seem to be another auto-immune disorder which can be induced by TNF $\alpha$  inhibitors. Mechanisms of inflammatory myopathies are very heterogeneous and some authors show that TNF $\alpha$  can play a role in these diseases. In fact, some animal models showed a central role of TNF $\alpha$  [31,32] but some other didn't [33]. Surprisingly, excessive production of TNF- $\alpha$  has been observed in some inflammatory myopathies [32], thus TNF- $\alpha$  inhibitors should treat myositis rather than exacerbate this disease. In literature, there is limited and variable experience with anti-TNF $\alpha$  inhibitors in the treatment of myositis. If some case reports and case series described improvement of myositis with TNF $\alpha$  inhibitors, randomized, controlled trials failed to confirm an interest of TNF $\alpha$  inhibitors in myositis treatment [34]. Indeed, one multi-center, open-label, controlled trial studying infliximab in patients with recent onset of myositis combined with weekly methotrexate was prematurely ended because of a low enrolment rate and a high drop-out rate due to disease progression or infusions reactions [35]. Moreover, 2 randomized controlled-trials failed to show efficacy of etanercept [36] or infliximab [37] in patients with dermatomyositis [36] or myositis [37]. The most common hypothesis to explain implication of TNF $\alpha$  inhibitors in inducing myositis is a disturbance of the cytokine balance related to TNF $\alpha$  inhibitors inducing myositis or other auto-immunes diseases [27,38]. Another mechanism, also described in literature, involve an increased production of auto-antibodies

by TNF- $\alpha$  inhibitors [27,38]. Genetic factors could also be involved because a polymorphism of TNF $\alpha$  has been showed to promote juvenile dermatomyositis [39].

Our collection of cases has many strengths: (i) the inflammatory nature of the muscle impairment was systematically proven by a muscle biopsy; (ii) secondary myositis related to viruses or neoplasms were mostly ruled out; (iii) chronological and semiological data strongly suggest a role of adalimumab; (iv) using national and international bases such as the FPVD or VigiBase® allow a larger vision, over a long period of time.

Nevertheless, our reports also have limits: (i) underreporting is a well-known flaw in spontaneous reporting systems. However, the spontaneous reporting system of ADR remains a useful tool in pharmacovigilance to generate signals of new or rare ADR; (ii) this is a retrospective study and data are sometimes missing; (iii) the causality cannot be certain as adalimumab was not reintroduced in most cases; (iv) we cannot rule out a myositis-like complication of the initial disease (protopathic biais).

### **Conclusion**

Adalimumab is largely used in inflammatory rheumatic and bowel diseases. If some frequent muscular adverse effects such as myalgia and muscle spasm are well-known and benign, inflammatory myopathies should also be considered in case of muscular symptoms as they can be severe. We believe this adverse effect should be mentioned in SmPC to alert healthcare professionals. Finally, more data are needed to study the possible role of other TNF $\alpha$  inhibitors in developing myositis.

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Table 1: Review of French Pharmacovigilance Database (- corresponds to missing data)

CASE N°	1 (our case)	2	3	4	5	6
<b>DEMOGRAPHY</b>						
Sex	Female	Female	Female	Female	Female	Male
Age (years)	63	61	60	56	37	36
Medical condition treated with adalimumab	Crohn's disease	Psoriasis	Rheumatoid arthritis	Ankylosing spondylitis	Inflammatory bowel disease and ankylosing spondylitis	Crohn's disease
<b>MUSCLE INVOLVEMENT</b>						
Clinical	Muscle weakness, dysphagia	Myalgia, muscle cramps, myoclonus	Muscle weakness	Myalgia	Muscle weakness	Myalgia
Time to onset	6 month	4 years	6 years	7 years	3 months	3 years
CK elevation – maximum value	Yes – 866 UI/L	Yes – 100 000 UI/L	Yes – 528 UI/L	Yes – 3000 UI/L	Yes – (51N)	Yes – not known
Electromyography	Myogenic, signs of necrosis	Myogenic, signs of necrosis, axonal neuropathy	Myogenic	Myogenic	Normal	Normal
<b>IMMUNOLOGY</b>						
Antinuclear antibody - Title	Yes – 1/640	Non significant – 1/80	Yes – 1/320	-	--	-
Myositis specific antibodies	No	No	No	No	No	No
<b>MUSCLE PATHOLOGY</b>						
Diameter of muscle fibers	Irregular	Irregular	-	Irregular	Irregular next to inflammatory foci	Irregular
Ragged red fibers	Yes	No	-	No	No	No
Endomysial infiltration by mononuclear cells	Yes, mostly T-cells (80-10%), slightly more CD4+ than CD8+	Yes, focal, by lymphocytes	Yes	Yes, one foci with macrophages and some lymphocytes	Yes, mostly CD8+ T-cells	Yes (not typed), granulomatous in one or two levels
Myonecrosis	Yes	Yes	Yes	-	Yes	Yes
Diffuse HLA-1 expression	Yes (predominating in atrophic foci)	Yes	-	Yes (predominantly perifascicular)	Yes (heterogeneous)	Yes (multifocal)
COX negative fibers	20%	Some	-	No	No	No
C5b-9	Muscle fibers, some capillaries	Many muscle fibers	-	Next to microthrombi	Capillaries	Necrotic muscle fibers only
Rimmed vacuoles	No	No	-	No	No	Yes
P62	Few inclusions	-	-	-	-	No
TDP43	Few inclusions	-	-	-	-	Some fibers
<b>MANAGEMENT</b>						
Other aetiologies excluded	Viral, paraneoplastic	Viral, paraneoplastic	No	Viral, paraneoplastic	Viral	Viral
Adalimumab stopped	Yes	Yes	Yes	Yes	Yes	Yes
Medical care	Corticosteroids	Corticosteroids	Corticosteroids and human immunoglobulins then rituximab	Corticosteroids and methotrexate	Corticosteroids then azathioprine and hydroxychloroquine	Corticosteroids
OUTCOME	Favourable	Unresolved	Stabilized	Improvement in progress	Stabilized	Favourable
PROBABILITY SCORE (Naranjo scale)	5 (probable)	3 (possible)	4 (possible)	4 (possible)	4 (possible)	6 (probable)