Autoimmunity Reviews 13 (2014) 1035–1041

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Long-term effectiveness and safety of interleukin-1 receptor antagonist (anakinra) in Schnitzler's syndrome: A french multicenter study

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ARTICLE INFO

Article history:
Received 16 May 2014
Accepted 3 June 2014
Available online 23 August 2014

Keywords:
Schnitzler's syndrome
IL-1 receptor antagonist
Autoinflammatory disease
Gammopathy
Urticaria

ABSTRACT

The aim of this study is to assess the long-term effectiveness and safety of IL1Ra in Schnitzler syndrome (SchS). Between 2010 and 2012, we performed a nationwide survey among French internal medicine departments to identify SchS patients. We retrospectively analyzed the long-term efficacy and safety of IL1Ra and the outcome of patients that did not receive this treatment. Forty-two patients were included in the study, 29 of whom received IL1Ra. The mean age at disease onset was 59.9 years. Disease manifestations included urticaria (100%), fever (76%), bone/joint pain (86%), bone lesions (76%), anemia (67%), and weight loss (60%). The monoclonal gammopathy was overwhelmingly IgM kappa (83%). The mean follow-up was 9.5 years (range: 1.6–35). Two patients developed Waldenström's macroglobulinemia and one developed AA amyloidosis. All of the 29 patients who received IL1Ra responded dramatically. After a median follow-up of 36 months (range: 2–79), the effectiveness remained unchanged. All patients remained on anti-IL-1 therapy. Twenty-four patients (83%) went into complete remission and five (17%) into partial remission. Three patients experienced grade 3–4 neutropenia. Six patients developed severe infections. No lymphoproliferative diseases occurred while on IL1Ra. When last seen,

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http://dx.doi.org/10.1016/j.autrev.2014.08.031

all patients without anakinra had an active disease with variable impact on their quality of life. Their median corticosteroids dosage was 6 mg/d (range: 5–25). IL1Ra is effective in SchS, with a sharp corticosteroid-sparing effect. Treatment failures should lead to reconsider the diagnosis. Long-term follow-up revealed no loss of effectiveness and a favorable tolerance profile. The long-term effects on the risk of hemopathy remain unknown.

Contents

1. Introduction

Schnitzler's syndrome (SchS) is a rare disease that manifests with a urticarial skin rash, monoclonal gammopathy (mostly IgM kappa), and a variable combination of recurrent fever, osteoarticular pain, sclerotic bone lesions, lymphadenopathy, and hepatosplenomegaly [1,2] This disease was first described by the French dermatologist Liliane Schnitzler almost 40 years ago [3,4], but even today it is still underdiagnosed [5].

Patients with SchS frequently exhibit an altered quality of life (QoL) because of recurrent fever, rash, pain, fatigue, and sometimes weight loss or anemia [1,2]. As with other patients with monoclonal gammopathy of undetermined significance, SchS patients may develop a hematological malignancy (usually Waldenström's macroglobulinemia). More infrequently, they can develop AA amyloidosis [6,7]. Conventional therapies, such as antihistamines, non-steroidal anti-inflammatory drugs (NSAID), corticosteroids, immunomodulating agents (colchicine and hydroxychloroquine), and pefloxacin, usually provide only partial or transient improvement of the symptoms [7]. Disease-modifying anti-rheumatic drugs are rarely useful [2,7]. In recent years, several case reports have revealed the remarkable efficacy of the interleukin-1 (IL-1) receptor antagonist (IL1Ra) anakinra on this disease [8,9]. Two small, open-label, non-comparative studies also demonstrated the short-term efficacy of the long-acting IL-1 blockers canakinumab [10] and rilonacept [11]. Given the efficacy of blocking IL-1 activity toward treatment of this disease, phenotypical similarities between SchS and cryopyrin-associated periodic syndrome, and biological data suggesting a dysfunction of the inflammasome [11–15], most physicians and scientists consider SchS an acquired, late-onset auto-inflammatory disease [1,2,7,16]. However, the relationship between the systemic inflammation and the monoclonal component remains unknown.

Unfortunately, most data regarding the use of IL1Ra in SchS arise from case reports or very small study series. Therefore, long-term data regarding its efficacy, tolerance, and safety are scarce. Furthermore, the concern that some patients may not respond to IL-1 blockers has recently emerged [17,18] and the possibility of secondary treatment failure remains unknown [2].

Herein we report on the long-term effectiveness and safety of the off-label use of IL1Ra in SchS through a retrospective analysis of a multicenter cohort of 42 patients with SchS, of whom 29 were treated with IL1Ra.

2. Patients and methods

2.1. Patients

In this study, we included all of the SchS patients evaluated at Nantes University Hospital since 1998 ($n = 17$). Further, we conducted a nationwide survey among all of the departments of internal medicine in France through the French Internal Medicine Society (Société Nationale Française de Médecine Interne) from 2010 to 2012. To be included, patients had to fulfill the diagnostic criteria proposed by Lipsker et al. in 2001 [19], irrespective of the recourse or the effect of IL-1 blockers. This observational study was performed in accordance with the Helsinki declaration, European and French ethical laws.

2.2. Data collection

Data were collected from charts using a standardized form that included the following information: gender, month/year of birth, date of first symptoms and diagnosis, disease manifestations, bone and thoracoabdominal imaging findings, previous therapies, significant comorbidities, clinico-biological features, concomitant treatments at the onset of IL1Ra use and at the last follow-up, secondary IL1Ra treatment failures, flare-ups following drug interruption or tapering, IL1Ra withdrawal and its reason(s), severe infections (requiring hospitalization), injection site reactions, neutropenia and any other IL1Ra adverse effects, solid or hematologic malignancy, death and cause of death.

2.3. Disease activity measurement and response to IL1Ra

Physician assessment of SchS clinical activity was recorded using a semi-quantitative scale for skin rashes, pain, and fever (absent/rare-moderate/frequent-severe). Moderate and severe anemia was defined as 10–12 and <10 g/dL hemoglobin levels, respectively. Complete