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Review

Biologics in myelodysplastic syndrome-related systemic inflammatory and autoimmune diseases: French multicenter retrospective study of 29 patients☆

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ABSTRACT

Background: Systemic inflammatory and autoimmune diseases (SIADs) associated with myelodysplastic syndromes are often difficult to treat. Corticosteroids are efficient but only usually at high doses. The use of biologics needs to be specified.
Methods: In a French multicenter retrospective study, we analyzed the efficacy and safety of biologics (tumor necrosis factor-α [TNF-α] antagonists, tocilizumab, rituximab and anakinra) for SIADs associated with myelodysplastic syndromes (MDSs). Clinical, biological and overall treatment responses were evaluated. When several lines of treatment were used, data were analyzed before and at the end of each treatment line and were pooled to compare overall response among steroids, disease-modifying anti-rheumatic drugs (DMARDs) and biologics.

☆ Conflicts of interest and funding: Arsene Mekinian and Olivier Fain are investigators of a Cellgene-sponsored trial.

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Corticosteroids
Biologics

Results: We included 29 patients (median age 67 years [interquartile range 62–76], 83% males) with MDS-related SIADs treated with at least one biologic. The MDSs were predominantly refractory anemia with excess blasts 1 (38%) and refractory cytopenia with multilineage dysplasia (21%). The SIADs were mainly arthritis ($n = 6$; 20%), relapsing polychondritis ($n = 8$; 30%) and vasculitis ($n = 10$; 34%). During a 3-year median follow-up (IQR 1.3–4.5), a total of 114 lines of treatments were used for all patients: steroids alone (22%), DMARDs (23%), TNF-α antagonists (14%), anakinra (10%), rituximab (10%), tocilizumab (7%) and azacytidine (9%). Considering all 114 lines, overall response (complete and partial) was shown in 54% cases. Overall response was more frequent with steroids (78%) and rituximab (66%) than DMARDs (45%) and other biologics (33%) ($p < 0.05$). Rituximab had better response in vasculitis and TNF-α antagonists in arthritis. During follow-up, 20 patients (71%) presented at least one severe infection.
Conclusion: This nationwide study demonstrates the efficacy of steroids for SIAD-associated MDSs but a high frequency of steroid dependence. The response to biologics seems low, but rituximab and azacytidine seem promising.

Contents

1. Introduction

In 15% to 20% of cases, myelodysplastic syndromes (MDSs) and chronic myelomonocytic leukemia (CMML) can be associated with systemic inflammatory and autoimmune diseases (SIADs) [1]. Treatment for MDS/CMML-related SIADs is challenging because of the underlying cytopenias and risk of infection. Steroid dependence is frequent and the use of steroid-sparing drugs, particularly cyclophosphamide, methotrexate and azathioprine, is limited because of the risk of secondary MDSs [1,2].

Data describing the value and safety of other immunomodulating drugs besides steroids are scarce, particularly disease-modifying antirheumatic drugs (DMARDs) and biologics. Biologics are largely used for SIADs without underlying MDSs/CMML, and tumor necrosis factor α (TNF-α) antagonists were used for MDSs without increasing the risk of leukemia transformation or cytopenias [3,4]. Only a few cases reported the interest of biologics in MDS-related SIADs, and large case-series in this topic are lacking [5–7]. We recently showed high SIAD response on treating MDSs with azacytidine in steroid-dependent/refractory disease, but these data remain to be confirmed [8].

In this French nationwide study, we report the long-term outcome of 29 patients with MDS/CMML-associated SIADs treated with biologics (TNF-α antagonists, tocilizumab, rituximab and anakinra) and compare the safety and efficacy of the drugs.

2. Patients and methods

2.1. Patients

We retrospectively collected data for patients with MDSs/CMML and SIADs followed between 2006 and 2016 in 16 French centers. Cases were recruited through the *Société Nationale Francaise de Médecine Interne* (SNFMI) and the *Club Rhumatismes Inflammation* (CRI). Inclusion criteria were SIADs with MDSs/CMML (WHO 2008 classification) treated with at least one biologic (TNF-α antagonists, tocilizumab, anakinra or rituximab) during follow-up. MDSs/CMML and SIADs had to be diagnosed concomitantly (within 5 years), and cases associated with infectious, treatment-related or neoplastic origin were excluded.

The study was performed in accordance with the ethical standards of the Helsinki Declaration.

2.2. Data collection

We collected data on age, sex, MDSs/CMML features (type, medullar blast number, International Prognostic Scoring System [IPSS] and IPSS-revised [IPSS-R], karyotype, specific treatments), SIAD features and treatments. For each line of SIAD treatment, clinical and biological data, steroid amounts and reasons for treatment discontinuation were recorded at the beginning and end of each line of treatment. The different lines of conventional immunosuppressive agents (DMARDs), biologics and specific MDS/CMML treatment (azacytidine) were analyzed separately for each patient.

SIAD treatment response was defined as clinical response (complete with disappearance of all symptoms or partial with at least 50% improvement) and biological response (C-reactive protein level normalization and/or at least 50% decrease in level). Treatment response was defined at 6 months after treatment initiation or at the time of switch to another drug. Remission was defined as complete clinical and biological response. Steroid dependence was defined as prednisone-equivalent amount >20 mg/day during at least 2 months. Relapse was defined as active disease after a remission period, which required change of the treatment regimen.