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Review

Biologics-induced autoimmune renal disorders in chronic inflammatory rheumatic diseases: Systematic literature review and analysis of a monocentric cohort

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ABSTRACT

The use of biologic drugs has been linked with the paradoxical development of systemic and organ specific autoimmune processes. The aim of this study was to describe the features of biologics-induced autoimmune renal disorders (AIRD) through a systematic review and a cohort study of 707 adult patients affected with Rheumatoid Arthritis (RA), Ankylosing Spondylitis (SA) and Psoriatic Arthritis (PsA).
The literature search identified 2687 articles of which 21 were considered relevant for the present study, accounting for 26 case reports. The cohort analysis retrieved 3 cases. According to clinical manifestations and kidney histology the identified AIRD cases were classified as: a) glomerulonephritis associated with systemic vasculitis (GNSV), b) glomerulonephritis in lupus-like syndrome (GNLS), c) isolated autoimmune renal disorders (IARD). Twenty-two out of 29 cases with AIRD were reported in patients affected by RA, 5 in AS and 2 in PsA. The biologic drug most frequently associated with development of AIRD was Etanercept (15 cases, 51.7%), followed by Adalimumab (9 cases, 31.0%) and Infliximab (3 cases, 10.3%) while Tocilizumab and Abatacept were reported in 1 case (3.4%) for each. Thirteen out of 29 (44.8%) cases were classified as affected by IARD, 12 (41.3%) as GNSV and 4 (13.9%) as GNLS. Worse prognosis was associated with GNSV and lack of biologic withdrawal. Although rare, AIRD may be life-threatening and may lead to renal failure and death. If AIRD occurs, biologic drugs must be stopped and patient should be treated according to clinical manifestations and kidney biopsy findings.

Contents

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1. Introduction

Biologic drugs are licensed for the treatment of chronic inflammatory rheumatic diseases (IRD) including Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA) and Ankylosing Spondylitis (AS). The introduction of anti-TNF-alpha agents has changed the treatment of these inflammatory conditions [1,2]. Afterwards, a better understanding of disease pathogenesis has led to the development of new-targeted biologic treatments for RA with different mechanisms of action. They act by inhibiting the effect of specific cytokines (IL1, IL6) or selectively targeting CD20-positive B cells or preventing antigen-presenting cells from delivering the co-stimulatory signal to T lymphocytes by binding to CD80 and CD86, thereby blocking interaction with CD28 [3]. Further treatment modalities are being investigated such as targeting IL-17 to modulate Th17/Treg balance and reduce inflammation [4].

Biologics are usually considered cost-effective in controlling disease activity, inhibiting the progression of structural damage and reduce the risk of co-morbidities such as osteoporosis in patients with chronic IRD [5–7]. On the other hand, all of these drugs have a range of shared adverse effects including the paradoxical development of autoimmune processes, ranging from asymptomatic immunologic alterations to life-threatening systemic autoimmune diseases [8]. The higher number of reports on the development of autoimmunity is related to the use of TNF-alpha-blocking agents, however other biologics have recently been associated with the development of systemic and organ specific autoimmune conditions [9]. Although unusual, biologics-induced autoimmune kidney damage has been reported in patients affected by chronic IRD as isolated disorder or as part of the spectrum of drug-induced Systemic Lupus Erythematosus (SLE) and drug-induced systemic vasculitis [8,9]. However, the clinical characteristics and outcomes of autoimmune renal disorders (AIRD) triggered by biological therapy have not been specifically addressed. The purpose of this study is to describe the features of biologics-induced AIRD in adult patients with chronic IRD through a systematic review and the analysis of a monocentric cohort followed-up in an Italian third level center of rheumatology.

2. Methods

2.1. Systematic review

Two investigators (MP, EC) performed a systematic review of the literature, according to the PRISMA guidelines, searching for articles published between the 1st of January 1990 and the 31st of January 2014 reporting on the development of AIRD (Outcome) in adult patients with IRD (Population) receiving biologics (Intervention). The following search strategy through MEDLINE via PubMed was designed using a combination of Mesh terms: ("Arthritis, Rheumatoid"[Mesh]) OR ("Spondylitis, Ankylosing"[Mesh]) OR ("Arthritis, Psoriatic"[Mesh]) AND ("Interleukin 1 Receptor Antagonist Protein"[Mesh]) OR ("infliximab" [Supplementary Concept]) OR ("TNFR-Fc fusion protein" [Supplementary Concept]) OR ("adalimumab" [Supplementary Concept]) OR ("golimumab" [Supplementary Concept]) OR ("certolizumab pegol" [Supplementary Concept]) OR ("rituximab" [Supplementary Concept]) OR ("tocilizumab" [Supplementary Concept]) OR ("abatacept" [Supplementary Concept]) AND ("Glomerulonephritis"[Mesh]) OR ("Nephrotic Syndrome"[Mesh]) OR ("Nephrosis, Lipoid"[Mesh]). Additional papers were obtained by checking the references from the selected studies as well as from review articles and other sources known to the authors. All type of studies were allowed, but only full publications reporting on adult patients and written in English were included in the literature search. Once investigators have independently selected the articles, initially on the basis of titles and abstracts then if necessary on the full texts, eligibility assessment was performed independently in a blinded standardized manner. Disagreements between reviewers were solved by consensus. Whenever papers reported duplicate data, the most recent article was selected. To be included in the review, the retrieved papers had to provide the descriptive features of each reported case of biologics-induced AIRD. In particular, demographic, clinical, histopathologic (if performed), treatment and outcome data must be provided. In an attempt to clarify if AIRD are specific adverse reactions for biologic drugs, the WHO-UMC system for standardized case causality assessment (http://who-umc.org/Graphics/24734.pdf) was applied and the reported adverse drug reactions were classified in a six categories scale ranging from "certain" to "unassessable/unclassifiable". Case reports classified in the last two categories of the scale, "conditional/unclassified" and "unassessable/unclassifiable", were excluded from the analysis of results. Causality assessment was performed independently in a blinded standardized manner by the two reviewers. Disagreements between reviewers were solved by consensus. When retrieved studies did not report the characteristics required for case classification we tried to contact the authors asking them to notify us the lacking features.

2.2. Longitudinal cohort analysis

The retrospective analysis of a prospectively followed-up population of adult with chronic IRD was performed. Data was retrieved using the database dedicated to patients treated with biological drugs at the Centre of Rheumatology of the University Hospital of Cagliari, Italy. For the purposes of the study, cases under investigation were defined as adult patients suffering from chronic IRD that had developed renal abnormalities following treatment with biotechnological drugs. The aim was to identify those patients that developed AIRD secondary to biologics treatment. Renal abnormalities were defined as: a) increased levels of blood urea nitrogen and serum creatinine; b) reduction of glomerular filtration rate; c) alterations of renal sediment (erythrocytes, leukocytes, casts); d) the appearance/worsening of proteinuria. To be included in the study a patient should have had blood tests and urine analysis at least three times per year and must have been followed-up for at least 12 months. Cases in which renal changes were explained by diseases (e.g. IRD by itself, infectious disease, diabetes, hypertension) or other drugs (e.g. gold salts, vaccination) were excluded. The diagnosis of AIRD was defined and reassessed according to kidney biopsy and clinical judgment. The WHO-UMC system for standardized case causality assessment was retrospectively applied to the identified cases. This study was performed according to the principles of Good Clinical Practice and the Declaration of Helsinki.

2.3. Case classification

According to clinical manifestations and kidney histology the identified cases were classified as: a) glomerulonephritis associated with systemic vasculitis (GNSV), b) glomerulonephritis in lupus-like syndrome (GNLS), c) isolated autoimmune renal disorders (IARD). Clinical outcomes were defined as i) complete resolution (i.e. inactive urinary