Canakinumab for refractory RA: a case report

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ABSTRACT

Rheumatoid arthritis is a common autoimmune disease leading often to joint destruction and reduced quality of life. We report a case of a young woman with rheumatoid arthritis with fever and rapid, destructive joint involvement verified with magnetic resonance imaging. She had failed therapy with methotrexate and leflunomide, anti-TNF, IL-6 inhibitor, B cell depletion and IL-1RA. Her laboratory results remained insignificant despite the aggressiveness of her disease. In this case, the patient only partly responded to anakinra but developed side effects, and therefore was switched to Canakinumab that led to sustained remission.

There are no clear biomarkers or other clues in order to separate early in the beginning of the disease course if a polyarticular inflammatory spectrum can be IL-1β driven. The young age of the patient at onset of disease, its aggressive course, inflammatory fever without significant laboratory inflammatory markers but with polyarthritis affecting small joints, may raise the suspicion of an IL-1β-driven disease and alert the treating rheumatologist to the use of IL-1β inhibitors early in the disease course.

INTRODUCTION

Rheumatoid arthritis is an autoimmune disease characterized by chronic inflammation of the joints. If untreated, it leads to destruction of the joints, severe disability and premature mortality.1 Apart from tumor necrosis factor (TNF), another proinflammatory factor implicated in the disease mechanism is interleukin 1 (IL-1). It causes inflammation and joint erosion and inhibits the tissue repair process shown in vitro.2 IL-1 induces production of matrix metalloproteinases (MMPs) that lead to cartilage destruction and bone resorption and causes synovial inflammation and pannus formation by promoting direct contact between macrophages and activated T-lymphocytes. It has therefore been considered a potential target for biologic Disease-Modifying Anti-Rheumatic Drugs (bDMARDs) such as Kineret (Anakinra®) and Canakinumab (Ilaris®).3

CASE DESCRIPTION

A 32-year old woman presented to the Rheumatology Outpatient Department of Henry Dunant Hospital Centre in Athens, Greece, in April 2014 suffering from polyarthritis (Figure 1). Her aunts from her father’s side and her grandfather suffered from rheumatoid arthritis and both her mother and sister had Hashimoto. The disease began in 2011 with fever and polyarthritis. At the time of presentation, she had already tried and
failed Methotrexate, Leflunomide, Etanercept, Golimumab, Infliximab and Tocilizumab.

Magnetic Resonance Imaging of the hands showed erosions, cysts and tenosynovitis (Figure 2). X-ray of the left wrist showed erosions of the styloid. It was then decided to change treatment to leflunomide (Arava®) 20 mg p.o.s in combination with Kineret (Anakinra®) 100 mg s.c. Due to disease progression, rituximab (Mabthera®) was then tried. The first infusion was given in November 2014, followed by the second infusion with a 2-week interval. At the follow-up visit after four months, deterioration of the synovitis in all the metacarpophalangeal (MCP) joints in both hands was noted.

As the young patient’s condition was not improving despite aggressive treatment, a change in mechanism of action was then considered. The clinical approach was that this rheumatoid arthritis, resistant to all above-mentioned therapy, maybe was more of auto-inflammatory origin; therefore more IL-1 driven than autoimmune. Ever since January 2016 IL-1b inhibitor Canakinumab (Ilaris®) was seriously considered. It was in April 2016 when Ilaris® was first administered. After the second subcutaneous injection, great improvement was mentioned regarding painful and swollen joints without any side-effects, situation unchanged even now.

DISCUSSION

IL-1 consists of two similarly structured parts (a and b) and has a functional receptor on all cell types, as well as a decoy receptor on neutrophils, monocytes and B lymphocytes. Its function is regulated in four different ways: by a true endogenous receptor antagonist (IL-1Ra), soluble receptors (IL-1sRII), a decoy receptor (IL-1 RII) and natural antibodies mostly to IL-1a. Pro-inflammatory IL-1 b is transformed to IL-1b through caspase-1 in inflammasome with properties on macrophages, keratinocytes, fibroblasts, mastocytes, endothelial and neuronal cells.

Synthesis and release of IL-1b depends on 2 consecutive signals. These are, in normal circumstances, started by damage-associated molecular patterns (DAMPs). These can either be pathogen associated-molecular patterns (PAMPs); for example, bacterial RNA or lipopolysaccharides, or irritants of the endogenous system, like uric acid or heat shock proteins. Synthesis of pro-IL-1b as well as components of the protein complex inflammasome NLRP3/cryopyrin is initiated by the first signal.
The second signal is needed for the assembly of the inflammasome and activates caspase-1, which consecu-
tively releases active IL-1b from pro-IL-1b. Canakinumab is a humanized monoclonal antibody
against IL-1b with peak concentration of 7 days and a
half-life of 22-33 days. A study of 472 patients with RA
revealed a best ACR20, 50 and 70 result with the admin-
istration of 150 mg subcutaneously every 4 weeks. The
authors used a predictive model of ACR response 30
months after a single administration of 2mg/kg canakin-
umab, namely 150mg subcutaneously. ACR 20 esca-
lated from 60% after one month to 70% in 30 months,
ACR 50 from 40 to 60% and ACR 70 from 30-40% re-
spectively according to this simulation of probability for
achieving ACR, converting the binary variables to cate-
gorical values; the results are significantly different from
placebo. Its efficacy as well as safety and tolerability are
established even in a 3-month phase II trial on RA pa-
patients.

The drug was approved for the treatment of auto-inflam-
matory diseases, mainly cryopyrin-associated periodic
syndromes, Adult Onset Still’s Disease (AOSD), Famil-
ial Mediterranean Fever (FMF), tumor necrosis factor
receptor–associated periodic syndrome (TRAPS), and
hyperimmunoglobulin D syndrome (HIDS/MKD), although its efficacy was also
studied in RA, DM2, COPD and age-related macular
degeneration.

IL-1 is even implicated in inflammatory
conditions considered comorbid to rheumatoid arthritis,
such as cardiovascular diseases and diabetes mellitus
type 2. Therapy with Canakinumab seems to be effec-
tive even in TNF-a failures, although long-term efficacy
in preservation of joint function is not known. It is there-
fore often used off-label in multiple indications. A recent
study from Italy investigating Anakinra and Canakinumab
use between 2008 and 2016 showed that the latter was
used in 56% of cases off-label in 105 treatment courses.
Seventy-six from a total of 475 treated patients (14.4%)
reported adverse events (AEs) and 10 (1.9%) serious ad-
verse events (SAEs), revealing a good safety profile of
these medicine.

In conclusion, aggressive rheumatoid arthritis in young
patients demands proper and efficient treatment in order
to avoid joint deformation. Despite aggressive treatment
with biologics, some patients continue to suffer. Canak-
umab can be a good option for those patients, and
can be used outside its known indications. It would be
useful to monitor these patients forward to estimate the
effect of the drug on disease proliferation and radiologic
progression in order to establish the best way for the pa-
tients to benefit from its use.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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