Seminars in Arthritis and Rheumatism 80 (2026) 153030

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

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

Long-term remission and monocyclic course in Still's disease patients starting canakinumab early: data from the international AIDA network registry

Antonio Vitale [a,b,*], Valeria Caggiano [a,b], Jessica Sbalchiero [a,b], Giuseppe Lopalco [c], Abdurrahman Tufan [d], Gaafar Ragab [e], Petros P Sfikakis [f], Lorenzo Dagna [g,h], Ezgi Deniz Batu [i], Seza Ozen [i], Fabrizio Conti [j], Federica Maiolini [k], Serena Bugatti [l], Micol Frassi [m], Piero Ruscitti [n], Andrea Cito [c], Ibrahim Yahya Cakir [d], Nergis Akay [o], Elif Kilic Konte [o], Katerina Laskari [f], Hulya Ercan Emreol [i], Roberta Priori [j], Jacopo Croce [k], Ludovico De Stefano [l], Crisafulli Francesca [l], Paola Cipriani [n], Francesco La Torre [p], Maria Cristina Maggio [q], Sulaiman M. Al-Mayouf [r], Lampros Fotis [s], Donato Rigante [t,u], Elena Verrecchia [u,v], Giuliana Guggino [w], Lidia La Barbera [w], Matteo Piga [x], Giacomo Emmi [y,z], Romina Gallizzi [aa], Giovanni Conti [ab], Paolo Sfriso [ac], Elena Bartoloni [ad], Roberto Giacomelli [ae,af], Patrizia Barone [ag], Maria Francesca Gicchino [ah], Annachiara Alemanno [a,b], Alberto Lo Gullo [ai], Haner Direskeneli [aj], Fatma Alibaz-Oner [aj], Anastasios Karamanakos [ak], Marcella Prete [al], Amr Edrees [am], Francesco Gavioli [a,b], Paola Parronchi [an], Francesco Ciccia [ao], Chiara Cardamone [ap], José Hernández-Rodríguez [aq], Gülen Hatemi [ar,as], Cemal Bes [at], Ibrahim A Almaghlouth [au,av], Ángel Robles Marhuenda [aw], Andrés Gonzáles-García [ax], Carla Gaggiano [a,b], Ilaria Mormile [ay], Mehmet Engin Tezcan [az], Antonio Luca Brucato [ba], Eugen Feist [bb,bc], Fernando Tornero-Romero [bd], Benoit Suzon [be], Benson Ogunjimi [bf,bg,bh,bi], Maissa Thabet [bj], Alessandro Conforti [bk], Valentina Pucino [bl], Oksana Boyarchuk [bm], Tetiana Kovalchuk [bm], Marcello Govoni [bn], Annamaria Iagnocco [bo], Maria Sole Chimenti [bp], Abdelhfeez Moshrif [bq], Emanuela Del Giudice [br], Francesco Carubbi [bs], Şükran Erten [bt], Samar Tharwat [bu,bv], Mohamed Tharwat Hegazy [e,bw], Ewa Więsik-Szewczyk [bx], Jiram Torres-Ruiz [by], Eduardo Martín-Nares [by], Alberto Balistreri [b,bz], Claudia Fabiani [b,ca], Bruno Frediani [a,b], Andrea Hinojosa-Azaola [by], Özgür Kasapçopur [o], Luca Cantarini [a,b,*]

[a] Department of Medical Sciences, Surgery and Neurosciences, Research Center of Systemic Autoinflammatory Diseases and Behçet's Disease Clinic, University of Siena, Siena, Italy
[b] Azienda Ospedaliero-Universitaria Senese [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center] Siena, Italy
[c] Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J) Policlinic Hospital, University of Bari, Bari, Italy
[d] Gazi University Hospital, Department of Internal Medicine, Division of Rheumatology, Ankara, Turkey
[e] Internal Medicine Department, Rheumatology and Clinical Immunology Unit, Faculty of Medicine, Cairo University, Giza, Egypt
[f] Joint Academic Rheumatology Program, Medical School, National and Kapodistrian University of Athens, [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center], Athens, Greece
[g] Faculty of Medicine, Università Vita-Salute San Raffaele, Milan, Italy
[h] Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy
[i] Division of Pediatric Rheumatology, Department of Pediatrics, Hacettepe University School of Medicine, Ankara, Turkey

* Corresponding authors at: Research Center of Systemic Autoinflammatory Diseases and Behçet's Disease Clinics, Department of Medical Sciences, Surgery and Neurosciences, University of Siena. Rheumatology Unit, Policlinico "Le Scotte", viale Bracci 16, 53100 Siena, Italy.
E-mail addresses: vitale.reumatologia@gmail.com (A. Vitale), cantariniluca@hotmail.com (L. Cantarini).

https://doi.org/10.1016/j.semarthrit.2026.153030

Available online 20 June 2026

[j] Department of Internal Medicine and Medical Specialties, Rheumatology Unit, AOU Policlinico Umberto I, Sapienza University of Rome, Viale del Policlinico 155, 00185 Rome, Italy
[k] Unit of Internal Medicine B, Department of Medicine, Università degli Studi di Verona, Verona, Italy
[l] Department of Internal Medicine and Therapeutics, Università di Pavia, Italy; Division of Rheumatology, Fondazione IRCCS Policlinico San Matteo, [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center], Pavia, Italy
[m] Rheumatology and Clinical Immunology, Spedali Civili and Department of Clinical and Experimental Sciences, University of Brescia, [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center], Brescia, Italy
[n] Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy
[o] Department of Paediatrics, Division of Paediatric Rheumatology, Istanbul University-Cerrahpasa, Faculty of Medicine, Istanbul, Turkey
[p] Department of Pediatrics, Pediatric Rheumatology Center (F.L.T.), Giovanni XXIII Pediatric Hospital, University of Bari Aldo Moro, Bari, Italy
[q] University Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (PROMISE) "G. D'Alessandro", University of Palermo, Palermo, Italy
[r] Department of Pediatrics, King Faisal Specialist Hospital and Research Center, College of Medicine, Alfaisal University, Riyadh, Saudi Arabia
[s] Department of Pediatrics, Attikon General Hospital, National and Kapodistrian University of Athens, Greece
[t] Department of Life Sciences and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[u] Periodic Fever Research Center, Università Cattolica Sacro Cuore, Rome, Italy
[v] Department of Aging, Neurological, Orthopedic and Head and Neck Sciences, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[w] Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, Rheumatology Unit, P. Giaccone University Hospital, University of Palermo, Italy
[x] Rheumatology Unit, Department of Medical Sciences and Public health, University and AOU of Cagliari, Cagliari, Italy
[y] Department of Medical, Surgical and Health Sciences, University of Trieste, Italy, and Clinical Medicine and Rheumatology Unit, Cattinara University Hospital, Trieste, Italy
[z] Centre for Inflammatory Diseases, Department of Medicine, Monash Medical Centre, Monash University, Clayton, VIC, Australia
[aa] Pediatric Rheumatology, Department of Health Sciences, Magna Graecia University, Catanzaro, Italy
[ab] Pediatric Nephrology and Rheumatology Unit, Azienda Ospedaliero Universitaria (AOU) G Martino, Messina, Italy
[ac] Rheumatology Unit, Department of Medicine, University of Padua, [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center], Padua, Italy
[ad] Rheumatology, Department of Medicine and Surgery, University of Perugia, Perugia, Italy
[ae] Clinical and Research Section of Rheumatology and Clinical Immunology, Fondazione Policlinico Campus Bio-Medico, Rome, Italy
[af] Rheumatology and Clinical Immunology, Department of Medicine, University of Rome Campus Bio-Medico, School of Medicine, Rome, Italy
[ag] Pediatric Rheumatology Unit, Department of Integrated Maternal-Child and Reproduction Activity, AOU "Policlinico-San Marco", Catania, Italy
[ah] Department of Woman, Child and General and Specialized Surgery, University of Campania "Luigi Vanvitelli", Naples, Italy
[ai] Unit of Rheumatology, Department of Medicine, ARNAS Garibaldi Hospital, Catania, Italy
[aj] Division of Rheumatology, Department of Internal Medicine, School of Medicine, Marmara University, Istanbul, Turkey
[ak] Department of Rheumatology, "Evangelismos" General Hospital, Athens, Greece
[al] Rheumatic and Systemic Autoimmune Diseases Unit, Department of Interdisciplinary Medicine (DIM), University of Bari Medical School, Bari, Italy
[am] Division of Rheumatology, University of Missouri, Kansas City, Missouri, USA
[an] Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
[ao] Department of Precision Medicine, Rheumatology Section, University of Campania Luigi Vanvitelli, Naples, Italy
[ap] UOC of Internal Medicine, Rheumatology Outpatients Unit, Azienda Ospedaliero-Universitaria San Giovanni di Dio e Ruggi D'Aragona, Salerno, Italy
[aq] Department of Autoimmune Diseases, Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Hospital Clínic of Barcelona, University of Barcelona, Barcelona, Spain
[ar] Department of Internal Medicine, Division of Rheumatology, Cerrahpasa Medical School, Istanbul University-Cerrahpasa, Istanbul, Turkey
[as] Behçet's Disease Research Center, Istanbul University-Cerrahpasa, Istanbul, Türkiye
[at] Department of Rheumatology, University of Health Sciences Başakşehir Çam and Sakura City Hospital, Istanbul, Turkey
[au] Rheumatology Unit, Department of Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia
[av] College of Medicine Research Center, College of Medicine, King Saud University, Riyadh, Saudi Arabia
[aw] Department of Internal Medicine, Autoimmune Disease Unit, Hospital Universitario La Paz, Madrid, Spain
[ax] Systemic Autoimmune Diseases Unit, Department of Internal Medicine, Hospital Universitario Ramón y Cajal, IRYCIS, Madrid, Spain
[ay] Department of Translational Medical Sciences, Section of Clinical Immunology, University of Naples Federico II, Naples, Italy
[az] Division of Rheumatology, Department of Internal Medicine, University of Health Sciences, Kartal Dr. Lutfi Kirdar City Hospital, Istanbul, Turkey
[ba] Department of Biomedical and Clinical Sciences, Fatebenefratelli Hospital, Università di Milano, Milan, Italy
[bb] Department of Rheumatology and Clinical Immunology, Helios Fachklinik Vogelsang-Gommern, Gommern, Germany
[bc] Experimental Rheumatology, Otto-von-Guericke Universität Magdeburg, Magdeburg, Germany
[bd] Autoimmune Diseases Unit, Department of Internal Medicine, Fundación Jiménez Díaz University Hospital, Madrid, Spain
[be] Department of Internal Medicine, Martinique University Hospital, Fort-de-France, Martinique
[bf] Antwerp Center for Translational Immunology and Virology (ACTIV), University of Antwerp, Antwerp, Belgium
[bg] Division of Paediatric Rheumatology, Department of Paediatrics, Antwerp University Hospital (UZA), Antwerp, Belgium
[bh] Division of Paediatric Rheumatology, Department of Paediatrics, Kidz Health Castle Universitair Ziekenhuis Brussel (UZB), Jette, Belgium
[bi] Division of Paediatric Rheumatology, Department of Rheumatology, Ziekenhuis Aan de Stroom (ZAS), Antwerp, Belgium
[bj] Internal Medicine Department, Farhat Hached University Hospital, Faculty of Medicine of Sousse, University of Sousse, Sousse, Tunisia
[bk] Ospedale San Paolo di Civitavecchia, U.O. Medicina Generale, ASL Roma 4, Civitavecchia, Rome, Italy
[bl] Clinical Immunology and Allergy Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
[bm] Department of Children's Diseases and Pediatric Surgery, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine
[bn] Rheumatology Unit, Department of Medical Sciences, Azienda Ospedaliero-Universitaria S. Anna-Ferrara, University of Ferrara, Ferrara, Italy
[bo] Academic Rheumatology Center, Dipartimento Scienze Cliniche e Biologiche, Università degli Studi di Torino, Turin, Italy
[bp] Rheumatology, Allergology and Clinical Immunology, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
[bq] Rheumatology Department, Faculty of Medicine, Al-Azhar University, Assiut, Egypt
[br] Department of Maternal Infantile and Urological Sciences, Sapienza University of Rome, Polo Pontino, Rome, Italy
[bs] Department of Life, Health and Environmental Sciences, University of L'Aquila; Internal Medicine and Nephrology Division, Avezzano-Sulmona-L'Aquila Local Health Authority 1, San Salvatore Hospital, L'Aquila, Italy
[bt] Department of Rheumatology, Ankara Bilkent City Hospital, Ankara Yıldırım Beyazıt University, Ankara, Turkey
[bu] Rheumatology and Immunology Unit (S.T.), Internal Medicine Department, Mansoura University, Mansoura, Egypt
[bv] Department of Internal Medicine (S.T.), Faculty of Medicine, Horus University, New Damietta, Egypt
[bw] Internal Medicine Department, Rheumatology Unit, Jahra Hospital, Kuwait
[bx] Department of Internal Medicine, Pneumonology, Allergology, Clinical Immunology and Rare Diseases, Military Institute of Medicine, National Research Institute, Warsaw, Poland
[by] Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico
[bz] Bioengineering and Biomedical Data Science Lab, Department of Medical Biotechnologies, University of Siena, Siena, Italy
[ca] Ophthalmology Unit, Department of Medicine, Surgery and Neurosciences, University of Siena, Italy

ARTICLE INFO

Keywords:
AOSD
Autoinflammatory disease
IL-1
Therapy
Treatment

ABSTRACT

Objectives: To evaluate whether early canakinumab initiation may provide treatment advantages in Still's disease (SD) patients, particularly in terms of therapy discontinuation due to long-term disease remission, glucocorticoid sparing effect, and increase in the frequency of monocyclic disease course rather than a polycyclic or chronic articular pattern.

Methods: SD patients treated with canakinumab were grouped according to time between disease onset and canakinumab initiation (≤3 months *vs.* >3 months). Patients were enrolled from the international Auto-Inflammatory Disease Alliance (AIDA) Network registry for SD.

Results: Overall, 190 patients were enrolled, 35 (19%) treated with canakinumab within three months from SD onset and 155 (82%) starting canakinumab later. Glucocorticoids use decreased more rapidly in patients receiving canakinumab within 3 months from SD onset than among patients treated later, with reductions of 50% vs 6% at month 3 (p=0.0001), and 75% vs 32% at month 6 (p=0.004). In logistic regression analysis, canakinumab initiation within 3 months from disease onset was significantly associated with treatment discontinuation due to long-term remission (OR 4.83, 95% CI 1.08-23.19; p=0.04). A monocyclic course occurred in 49% of patients starting canakinumab ≤3 months versus 8% starting later (p<0.0001). Starting canakinumab within 3 months from disease onset was significantly associated with a monocyclic disease course compared with the chronic-articular (RRR 4.43, 95% CI 1.12-17.60; p=0.034) and polycyclic courses (RRR 8.97, 95% CI 1.29-62.3; p=0.03).

Conclusions: Early canakinumab initiation is associated with treatment discontinuation due to long-term remission and appears linked to a greater frequency of a monocyclic disease course.

Introduction

Inhibition of interleukin (IL)-1 has proven to be an effective and safe therapeutic strategy in patients with Still's disease (SD). However, the optimal therapeutic approach within the framework of personalized and precision medicine still lacks important details. In particular, it remains unclear whether a true *therapeutic window of opportunity* exists for IL-1 inhibition, within which treatment initiation may lead to superior outcomes, or whether delaying therapy beyond a certain time point may be associated with disadvantages.

Still's disease is classically described as following three distinct disease course patterns, namely monocyclic, polycyclic, and chronic articular. The monocyclic pattern is characterized by a single inflammatory episode lasting up to twelve months, followed by sustained remission; it is generally associated with a favourable prognosis. The polycyclic pattern involves recurrent flares alternating with periods of remission, often requiring ongoing therapy to prevent relapses. In contrast, the chronic articular pattern is marked by persistent disease with prominent polyarthritis and risk of joint damage and is thought to reflect a shift toward adaptive immunity-driven mechanisms, with implications for treatment responsiveness [1].

A window of opportunity for early IL-1 blockade in Still's disease may exist, as the disease is thought to follow a biphasic course, evolving from an early autoinflammatory phase predominantly driven by innate immune mechanisms to a later chronic phase in which adaptive immune responses and persistent structural joint involvement become more prominent [2]. IL-1 is a key mediator of the early inflammatory cascade [3]; therefore, its inhibition is expected to be most effective during this initial phase, when the disease process is primarily cytokine-driven and potentially more reversible. In this context, early IL-1 inhibition might modulate the inflammatory trajectory and potentially attenuate progression towards chronic articular disease. Clinically, this could translate into more robust therapeutic responses and improved likelihood of sustained disease control when treatment is initiated early in the disease course [4]. However, the existence, magnitude, and duration of such a therapeutic window remain uncertain. According to Saccomanno et al. [5], anti–IL-1 therapy should be initiated within 3.9 years from symptom onset, whereas other real-life studies suggest IL-1 inhibitors are highly effective regardless of treatment timing. Specifically, starting the IL-1 receptor antagonist anakinra within or after 6 or 12 months, or as first-line biologic rather than after conventional disease modifying anti-rheumatic drugs (cDMARDs) or other biologic agents, did not significantly impact overall response. Nevertheless, faster control of systemic inflammation and resolution of articular manifestations have been reported with early IL-1 inhibition. In addition, smaller reductions in the systemic Pouchot score were observed in patients treated after prior cDMARDs or biologics [6]. Similarly, the selective anti–IL-1β monoclonal antibody canakinumab showed no significant differences in response across different biologic treatment lines [7] or SD courses (monocyclic, polycyclic, chronic articular) as described by Cush et al. [8].

The concept of a "window of opportunity" is most firmly established in other systemic inflammatory diseases with joint involvement, as for rheumatoid arthritis (RA), where initiation of disease-modifying anti-rheumatic drugs (DMARDs) within approximately 3-6 months of symptom onset can prevent irreversible joint damage in a substantial proportion of patients and fundamentally alter the disease course [9, 10]. This RA paradigm is particularly relevant to Still's disease, as both conditions appear to involve a transition between distinct pathogenic phases. In RA, the sequence progresses from preclinical autoimmunity to clinical synovitis and ultimately structural joint damage, whereas in Still's disease a comparable shift has been proposed from an early innate immunity-driven autoinflammatory phase to a later adaptive immunity-dominated chronic arthritic phase.

Taken together, the efficacy of IL-1 inhibitors appears to be robust and largely independent of the timing of treatment initiation. However, it remains crucial to determine whether early initiation may confer additional advantages, such as higher rates of sustained clinical inactive disease, greater corticosteroid-sparing effects, induction of a monocyclic disease course, or a more pronounced reduction in steroid exposure.

Therefore, the aim of the present study is to evaluate whether early initiation of IL-1 inhibition, defined by a disease duration cut-off of 3 months, provides treatment advantages compared with later initiation, particularly in terms of therapy discontinuation due to long-term disease remission, steroid sparing effect, and increase in the frequency of monocyclic disease course rather than a polycyclic or chronic articular pattern. To minimize variability associated with the use of different molecules, the present study was specifically restricted to patients receiving canakinumab.

Material and methods

Patients with SD fulfilling the Yamaguchi [11] and/or Fautrel [12] classification criteria and treated with canakinumab were enrolled.

Patients were divided into two groups according to the time from SD onset to canakinumab initiation: ≤3 months (group 1) and >3 months (group 2).

Patients were consecutively enrolled from the AIDA registry between June 2021 and November 2025. Follow-up duration varied across patients and was accounted for in the models when appropriate. Inclusion criteria comprised fulfillment of the Yamaguchi criteria or the Fautrel criteria [11,12], provision of informed consent to participate in the study, and treatment with canakinumab at the on-label dosage during the clinical course for the management of Still's disease. Exclusion criteria comprised prior use of the alternative IL-1 inhibitor, anakinra, in adult patients treated with canakinumab after 3 months from SD onset at a weight-adjusted dose (1-2 mg/kg/day, as for on-label schedule). In contrast, adult patients treated with anakinra at a fixed dose of 100 mg/day were included provided that their body weight exceeded 50 kg, as this dosing regimen was considered potentially indicative of partial IL-1 inhibition. Such an exclusion criterium accounted for the ruling out of 24 patients. Missing key data were also considered an additional exclusion criterion. Fig. 1 illustrates the flow diagram of patient inclusion and exclusion.

The primary aim of the study was to determine whether starting canakinumab as first line therapy within three months from SD onset was associated with benefits in terms of steroid sparing, reduced immunosuppressive burden, the possibility of treatment discontinuation due to long-term effectiveness, and a higher frequency of a monocyclic disease course. The secondary aim was to determine whether initiation of canakinumab later than three months after disease onset was associated with worse outcomes, as measured by the frequency of complete response at three months from canakinumab start and during the entire follow-up.

The exposure of interest was timing of canakinumab initiation, defined as early (≤3 months from disease onset) versus late (>3 months). The primary and secondary outcomes are detailed below and included measures of treatment response, glucocorticoid use, treatment discontinuation, and disease course. In particular, the primary endpoints of the study were: (i) the proportion of patients discontinuing glucocorticoids at 3, 6, and 12 months after initiation of canakinumab treatment and at the last assessment; (ii) the proportion of patients still requiring glucocorticoids at 3, 6, and 12 months after initiation of canakinumab treatment and at the last assessment; (iii) the reduction in daily glucocorticoid dose (prednisone or equivalent) between canakinumab initiation and the 3-month assessment; (iv) the frequency of concomitant use of conventional disease-modifying antirheumatic drugs (cDMARDs) to support canakinumab effectiveness over time; (v) the frequency of canakinumab discontinuation due to inefficacy, partial efficacy, or long-term disease control; (vi) the proportion of patients classified as having a monocyclic rather than a polycyclic or chronic-articular disease course, as defined by Cush et al [8]. The secondary endpoints were: (i) the frequency of complete response during canakinumab treatment; (ii) the capability of achieving complete response versus treatment failure; (iii) the systemic activity score according to Pouchot et al. or Rau et al. [13,14], recorded after three months of canakinumab administration; (iv) the proportion of patients achieving a systemic activity score of zero within three months of canakinumab initiation.

The definition of complete response adhered to the definition of inactive disease according to the EULAR/PReS recommendations [15], namely the absence of SD-related symptoms and normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. Partial response was defined as a substantial clinical and laboratory improvement, with near-complete resolution of clinical manifestations and normalization of inflammatory markers. All other cases were classified as treatment inefficacy.

Clinical, treatment and laboratory data were obtained from the International AutoInflammatory (AIDA) Network registry dedicated to SD. This is an ambidirectional study collecting both retrospective data accrued up to the time of inclusion in the Registry and prospective data related to disease progression and treatment thereafter. The Registry is not population-based, and data collection is performed by physicians participating in the AIDA project during or immediately after clinical

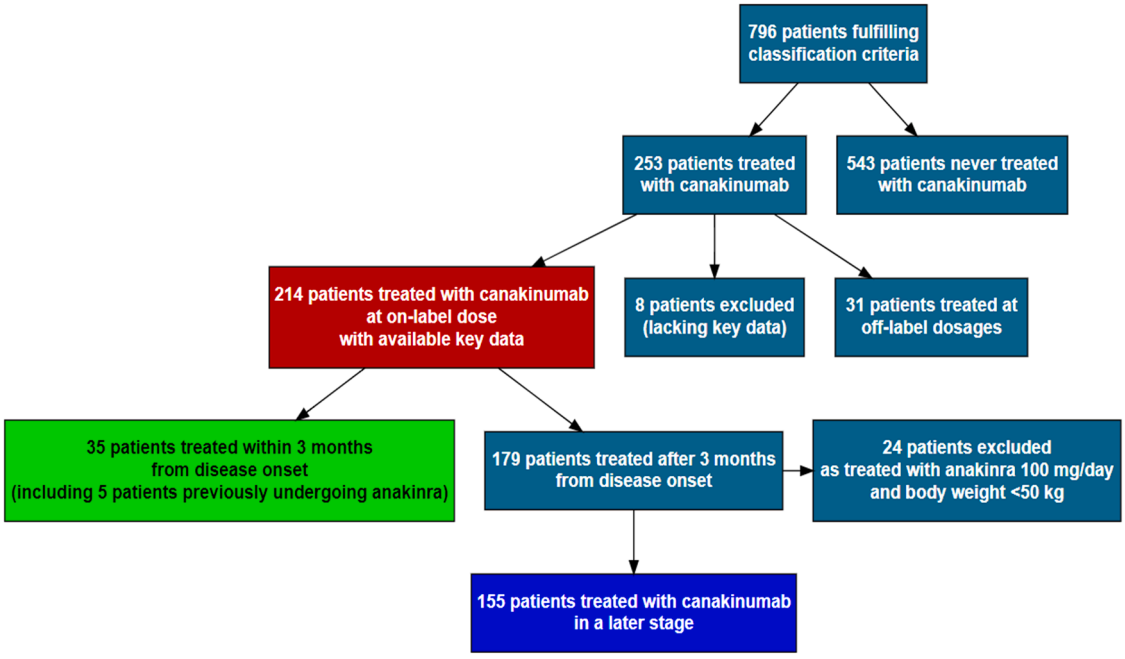

Fig. 1. Flow diagram of patient selection and treatment allocation.
Among 796 patients fulfilling classification criteria, 253 received canakinumab, of whom 214 were treated at the on-label dose. Patients not treated with canakinumab (n=543), those with missing key data (n=8), and those receiving off-label dosages (n=31) were excluded from the main analytical cohort. Treated patients were further stratified according to timing of treatment initiation, with 35 patients treated within 3 months from disease onset and 179 after 3 months. In this latter group, 24 patients were excluded because they had previously been treated with anakinra 100 mg/day while weighing <50 kg (a sufficient on-label dose: 1-2 mg/Kg/die). As a result, the group treated with canakinumab beyond the third month consisted of 155 patients.

visits. The collected data include demographic, clinical, laboratory, and therapeutic variables, as described in detail elsewhere [16].

The present study was approved by the Ethics Committee of Azienda Ospedaliero Universitaria Senese, Siena, Italy (AIDA Project; Ref. N. 14,951), as part of the AIDA program. The study protocol conformed to the tenets of the Declaration of Helsinki, and informed consent was obtained from all patients or their next of kin at the time of recruitment to the AIDA Registry dedicated to SD.

Descriptive statistics included mean and standard deviation or median and interquartile range (IQR), as appropriate according to data distribution, which was assessed using the Shapiro-Wilk test. Associations between study endpoints and early (≤3 months) versus late canakinumab initiation were evaluated using linear, binary, or multinomial logistic regression as appropriate. Linear regression results are reported as beta coefficients with 95% confidence intervals. Odds ratios (ORs) and relative risk ratios (RRRs) were obtained by exponentiating the beta coefficients from binary and multinomial logistic regression models, respectively, and are presented with 95% confidence intervals. Each endpoint was analyzed separately, with treatment timing coded as a dummy independent variable. All models were adjusted for paediatric versus adult onset and disease course (monocyclic, polycyclic, chronic-articular). Models assessing outcomes at the last assessment were adjusted for the total time of canakinumab treatment duration. Models assessing steroid reduction at 3 months were additionally adjusted for baseline glucocorticoids dose. Model assumptions were considered during model specification, and model stability was evaluated through convergence diagnostics. In logistic regression models, Firth's penalized method was applied in cases of complete separation to ensure robustness of estimates. Completeness of follow-up was ensured through continuous data entry. In addition, data completeness was assessed at the time of analysis, and analyses were conducted on available cases. Patients with missing data on key variables required for specific endpoints were excluded from the analyses. Missing data were not imputed, and analyses were conducted on available cases. Statistical significance was set at $p < 0.05$ (two-sided). Analyses were performed using R.

Results

Overall, 190 patients treated with canakinumab were enrolled. In 35 cases (18%), treatment was initiated within 3 months of SD onset. Anakinra had been used before canakinumab in 5 (22%) patients in the early IL-1 canakinumab group and in 23 (15%) patients in the late canakinumab group. Table 1 provides demographic and therapeutic details from patients treated with canakinumab before (group 1) and after (group 2) 3 months from SD onset.

Effectiveness

Complete response was observed in 21 (60%) patients in group 1 and 89 (57%) in group 2 (p=0.43). A partial efficacy was reported in 4 (11%) cases in group 1 and 37 (24%) cases in group 2 (p=0.23); inefficacy was reported in 2 (6%) cases in group 1 and 5 (3%) in group 2 (p=0.76).

In multinomial analysis, canakinumab initiation within 3 months was not significantly associated with complete (RRR 1.162, 95% CI 0.175-7.7; p=0.88) or partial response (RRR 0.612, 95% CI 0.08-4.97; p=0.65), using inefficacy as the reference.

Fig. 2 and Supplementary table 1 report regression analyses on treatment timing and systemic activity at three months, including the capability of achieving a systemic score of zero.

Steroid use

The median steroid dosage at the start of canakinumab therapy was 25 mg/day (IQR: 45) in group 1 and 10 mg/day (IQR: 15) in group 2 (p=0.22). Table 1 summarizes the mean daily dosage at 3 months and at the last assessment.

Table 1
Clinical, demographic and treatment features in Still's disease patients distinguished according to the time of canakinumab introduction: Group 1 refers to patients starting canakinumab within three months from disease onset and Group 2 refers to patients starting canakinumab later. Denominators for canakinumab dosage reflect available data at each time point. Median glucocorticoid doses were calculated only among patients receiving corticosteroid therapy at the corresponding time point. All analyses are based on available data without imputation. All comparisons between groups are unadjusted (crude) descriptive analyses. *Abbreviations: IQR, interquartile range. Unless otherwise specified, values are presented as absolute numbers, with percentages shown in parentheses.*

	Group 1 (n=35)	Group 2 (n=155)	p-value
Disease duration at start of canakinumab in months, median (IQR)	2 (2)	35 (65.5)	<0.001
Total canakinumab treatment duration in months, median (IQR)	16 (36)	27.5 (38.5)	0.03
Canakinumab dosage at start			
150 mg/4 weeks	6/31 (19%)	50/133 (38%)	0.09
300 mg/4 weeks	14/31 (45%)	55/133 (41%)	0.85
4 mg/Kg/4 weeks[#]	11/31 (36%)	28/133 (21%)	0.14
Canakinumab dosage at month 3			
150 mg/4 weeks	5/26 (19%)	42/115 (37%)	0.14
300 mg/4 weeks	15/26 (58%)	55/115 (48%)	0.50
4 mg/Kg/4 weeks[#]	6/26 (23%)	18/115 (16%)	0.53
Canakinumab dosage at last visit			
150 mg/4 weeks	9/35 (26%)	36/155 (23%)	0.93
300 mg/4 weeks	11/35 (31%)	61/155 (39%)	0.50
4 mg/Kg/4 weeks[#]	15/35 (43%)	58/155 (37%)	0.69
Global response to canakinumab			
Complete response	21 (60%)	89 (57%)	0.43
Partial efficacy - reduced frequency of flares and reduced severity of clinical/ laboratory manifestations	3 (9%)	19 (12%)	0.77
Partial - reduced severity of clinical/ laboratory manifestations	1 (3%)	14 (9%)	0.48
Partial - reduced frequency of flares	0 (0%)	4 (3%)	1.0
Inefficacy	2 (6%)	5 (3%)	0.62
Canakinumab discontinuation	11 (31%)	32 (21%)	0.17
Due to long-term remission	9 (26%)	9 (6%)	0.0009
Due primary inefficacy	2 (6%)	12 (8%)	1.00
Due to secondary inefficacy	0 (0%)	2 (1%)	1.00
Steroid use			
Steroid dose at the start of canakinumab in mg/day	10 (IQR: 15)	25 (IQR: 45)	0.22
Steroid dose at 3 months of canakinumab in mg/day	7 (IQR: 10)	6.5 (IQR: 5)	0.86
Steroid dose at the last assessment in mg/ day	5 (IQR: 3.75)	5 (IQR: 10)	0.12
Steroids taken at baseline	16 (46%)	65 (42%)	0.83
Steroids taken at month 3	8 (23%)	61 (39%)	0.10
Steroids taken at month 6	4 (11%)	44 (28%)	0.051
Steroid taken at month 12	3 (9%)	23 (15%)	0.42
Steroid taken at the last assessment	4 (11%)	27 (17%)	0.46
Use of concomitant cDMARDs	**8 (23%)**	**42 (27%)**	**0.76**
Methotrexate	8 (23%)	36 (23%)	1.00
Cyclosporine	0 (0%)	4 (3%)	0.76
Hydroxychloroquine	0 (0%)	1 (1%)	1.00
Leflunomide	0 (0%)	1 (1%)	1.00
Activity scores			
Systemic score[*] (Pouchot et al) at 3 months, median (IQR)	1 (2)	1 (1.5)	0.56
Systemic score (Pouchot et al) at 3 months equal to zero	29 (83%)	114 (74%)	0.35
Modified systemic score[*] (Rau et al) at 3 months	1.5 (2)	1 (2)	0.67
Modified systemic score (Rau et al) at 3 months equal to zero	29 (83%)	116 (75%)	0.43

[#] For pediatric patients, dosing was administered at the on-label regimen of 4 mg/kg every 4 weeks. In adults and adolescents with higher body weight, dosing was administered as fixed doses (150 mg or 300 mg every 4 weeks), approximating the on-label regimen of 4 mg/kg every 4 weeks.

[*] Among patients not achieving a score of zero.

In linear regression analysis, initiation of canakinumab within 3 months of disease onset was associated with a greater reduction in corticosteroid dosage compared with later initiation (β=17.48, 95% CI 5.35-29.61; p=0.007), indicating a larger adjusted between-group difference in steroid sparing at 3 months. At the last follow-up, no significant difference was observed in steroid reduction between groups (β=3.40; IC 95% -4.23 to 11.03; p=0.303).

Fig. 2 and Supplementary table 1 summarise the results from regression analysis investigating the associations between the early use of canakinumab and the glucocorticoid sparing effect.

The number of patients requiring corticosteroids at each time point is reported in Table 1. At month 3, corticosteroid use decreased by 50% in group 1 (from 16 to 8 patients) and by 6% in group 2 (from 65 to 61 patients, 4/65 patients; p=0.0001). At month 6, reductions were 75% in group 1 (4/16 patients) and 32% in group 2 (44/65 patients; p=0.004). At month 12, decreases were 81% (13/16 patients) and 65% (42/65 patients) in groups 1 and 2, respectively (p=0.25), while at the last follow-up, reductions were 75% in group 1 (12/16 patients) and 59% in group 2 (38/65 patients; p=0.15). These findings are graphically represented in Fig. 3.

Concomitant cDMARDs

Concomitant cDMARD use was observed in 50 (26%) patients during canakinumab treatment. In 36 (19%) cases, cDMARDs were already in use at the initiation of canakinumab. In the remaining 14 cases, cDMARDs were introduced to support canakinumab efficacy; in 12 out of 14 cases (86%), the additional use of cDMARDs induced clinical benefit. Notably, all such additions occurred in patients who initiated canakinumab after the third month of disease onset. Fig. 2 and Supplementary table 1 provide details from regression analysis looking for associations between early canakinumab initiation and cDMARDs use.

Concomitant cDMARDs were interrupted in 18/50 cases (36%) due to adverse events in 5/18 cases (28%), unsatisfying treatment response in 2 cases (11%), and long-term benefit in 2 cases (11%). The cause of cDMARDs withdrawal was not reported in 9 cases.

Canakinumab discontinuation

Table 1 reports the frequency and reasons for canakinumab discontinuation over time during a median follow-up of 16 months in group 1 and 35 months in group 2. In logistic regression analysis, initiation of canakinumab within 3 months of disease onset was significantly associated with treatment discontinuation due to long-term remission (OR 4.83, 95% CI 1.08-23.19; p=0.04), after adjustment for age at disease onset, disease course, and total treatment duration. No significant associations were observed for discontinuation due to primary failure (OR 1.44, 95% CI 0.17-8.73; p=0.701) or secondary failure (OR 1.68, 95% CI 0.59-5.53; p=0.39). Fig. 4 illustrates canakinumab discontinuation by reason and timing, and the association of early canakinumab initiation with discontinuation due to long-term remission.

Patients were classified according to disease course as follows: a monocyclic course was observed in 17 cases (49%) among those who initiated canakinumab within 3 months of SD onset, compared with 12 cases (8%) in the group starting canakinumab later (p < 0.0001). A

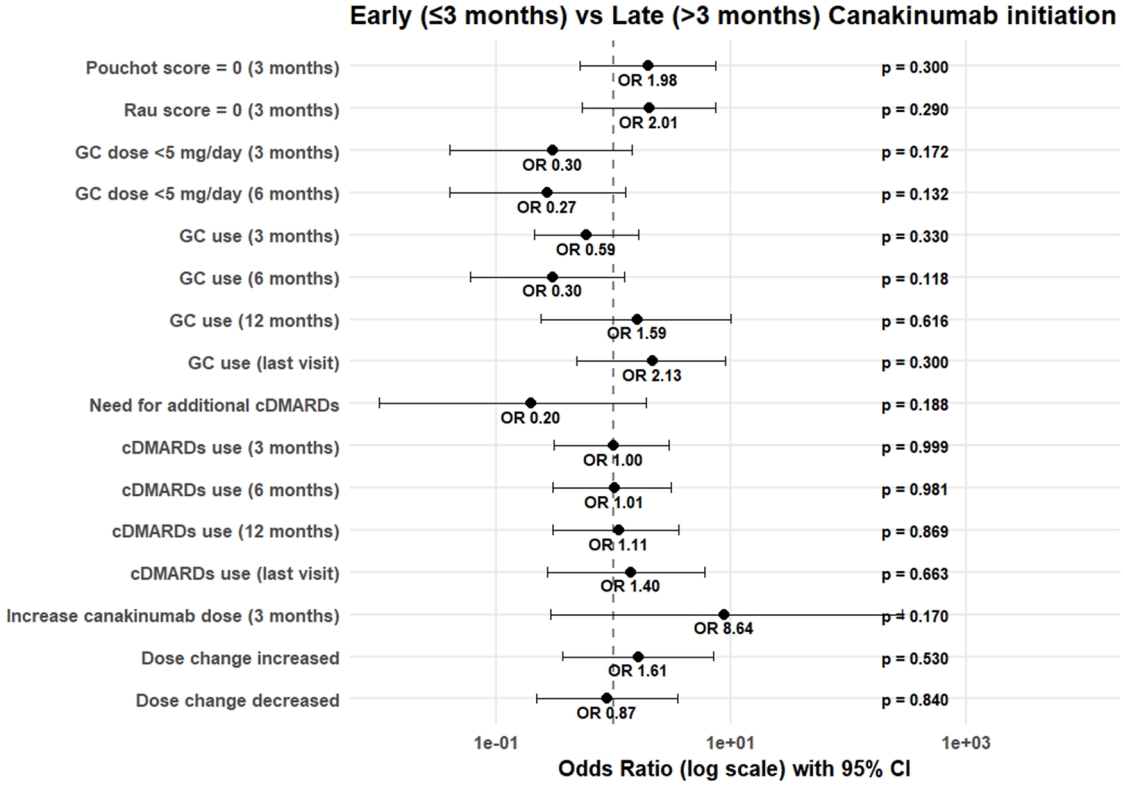

Fig. 2. Forest plot of regression analyses evaluating the association between early initiation of canakinumab (≤3 months from the start of canakinumab) and clinical outcomes in Still's disease. Outcomes include glucocorticoid (GC) use and tapering, use of concomitant conventional disease-modifying antirheumatic drugs (cDMARDs), and changes in canakinumab posology during follow-up. Odds ratios (ORs) with 95% confidence intervals (95% CI) are shown on a logarithmic scale, together with corresponding p-values. The vertical dashed line indicates the null effect (OR = 1). Models were adjusted for age at disease onset (paediatric vs adult) and disease course; additional adjustments were applied for treatment duration in analyses at last follow-up and for baseline GC dose in analyses of GC reduction at 3 months.

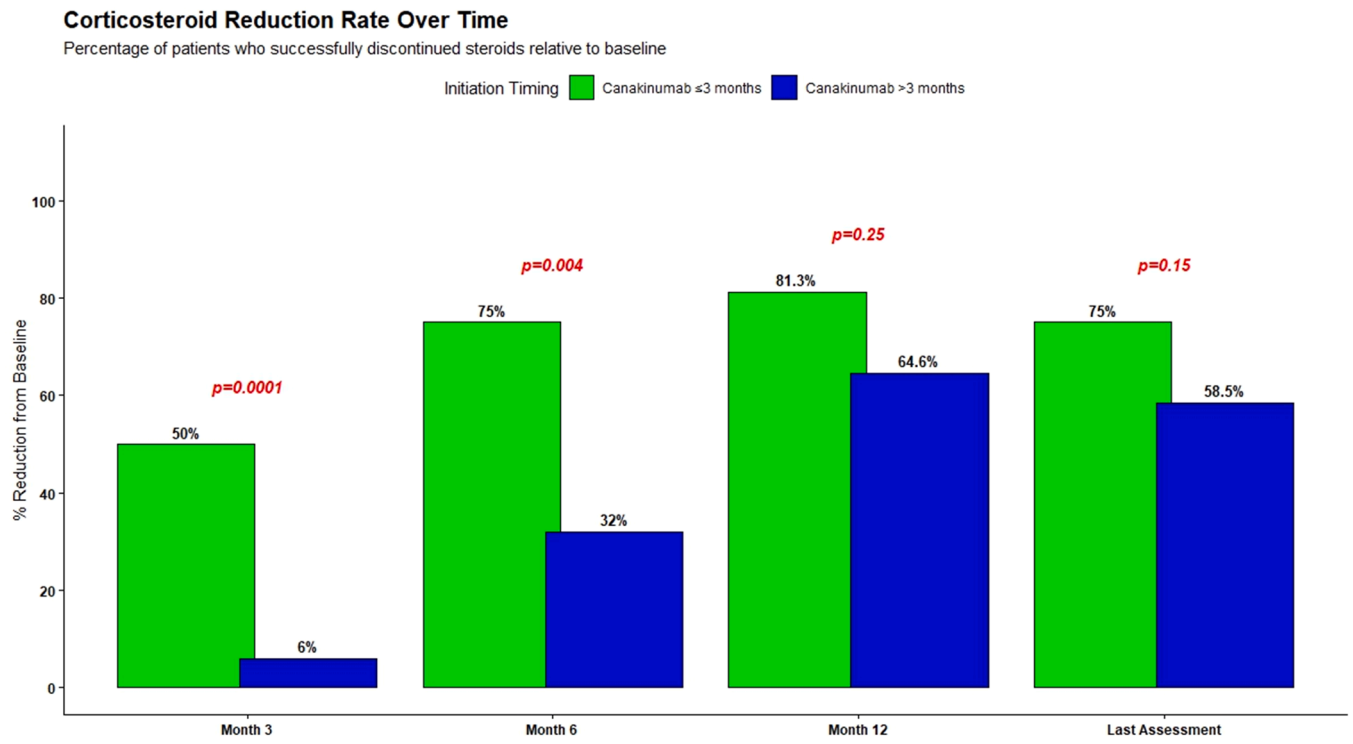

Fig. 3. Glucocorticoid sparing effect according to canakinumab initiation timing. Proportion of patients successfully discontinuing glucocorticoids at 3, 6, 12 months, and at the last assessment, relative to those receiving steroids at baseline. Data are stratified by early canakinumab initiation (≤3 months from disease onset, green bars) versus delayed initiation (>3 months, blue bars). Early canakinumab introduction was associated with significantly higher rates of steroid discontinuation at month 3 and month 6, while the effect reduced at later assessments.

polycyclic course was observed in 8 cases (23%) in the early-start group and in 75 cases (48%) in the late-start group (p=0.01). The chronic articular course was reported in 6 patients (17%) starting canakinumab early and 34 cases (22%) starting later (p=0.69). Disease course could not be classified in 4 cases (11%) in the early-start group and 34 cases (22%) in the late-start group (p=0.24).

Starting canakinumab within 3 months of disease onset was significantly associated with classification as a monocyclic disease course compared with the chronic-articular (RRR 4.43, 95% CI 1.12-17.60; p=0.034) and polycyclic courses (RRR 8.97, 95% CI 1.29-62.3; p=0.03). Fig. 5A illustrates the unadjusted distribution of disease course according to canakinumab initiation timing, while Fig. 5B shows the adjusted multinomial regression analysis demonstrating the association between early canakinumab initiation and monocyclic disease course.

Discussion

The present study is consistent with previous evidence indicating that the overall efficacy of canakinumab does not substantially depend

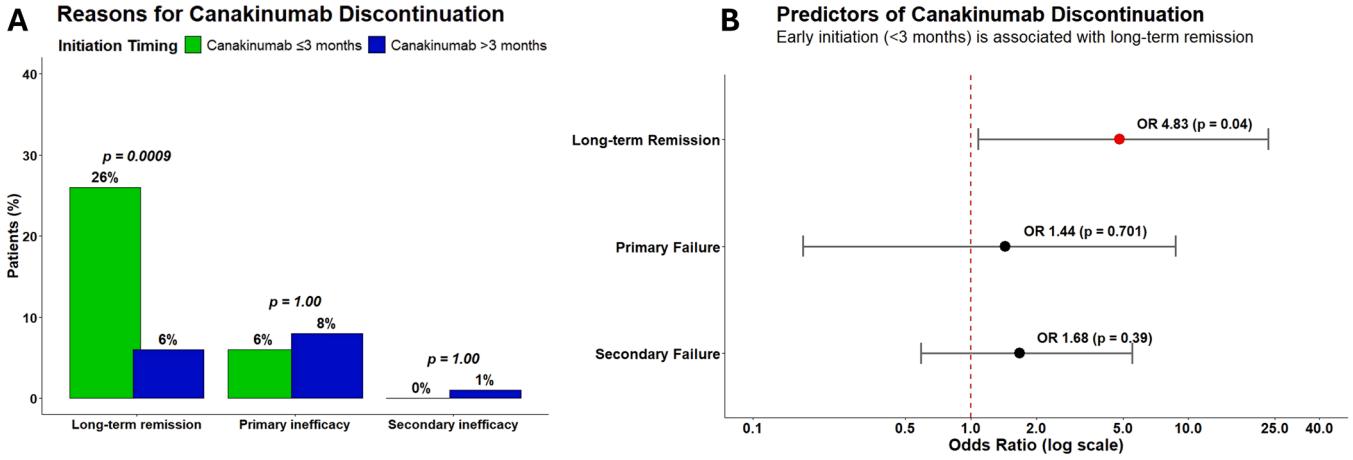

Fig. 4. Impact of canakinumab initiation timing on treatment discontinuation and association with long-term disease remission as a cause of canakinumab withdrawal. (A) Proportion of patients discontinuing canakinumab, categorized by reason (long-term disease remission, primary inefficacy, or secondary inefficacy), comparing early initiation (≤3 months from disease onset; green bars) versus late initiation (>3 months; blue bars). P-values indicate differences between the two groups for each reason, calculated using the chi-squared test or Fisher's exact test. (B) Forest plot showing odds ratios (ORs) and 95% confidence intervals (CIs) from binary logistic regression evaluating early canakinumab initiation as a predictor of treatment discontinuation due to long-term remission.

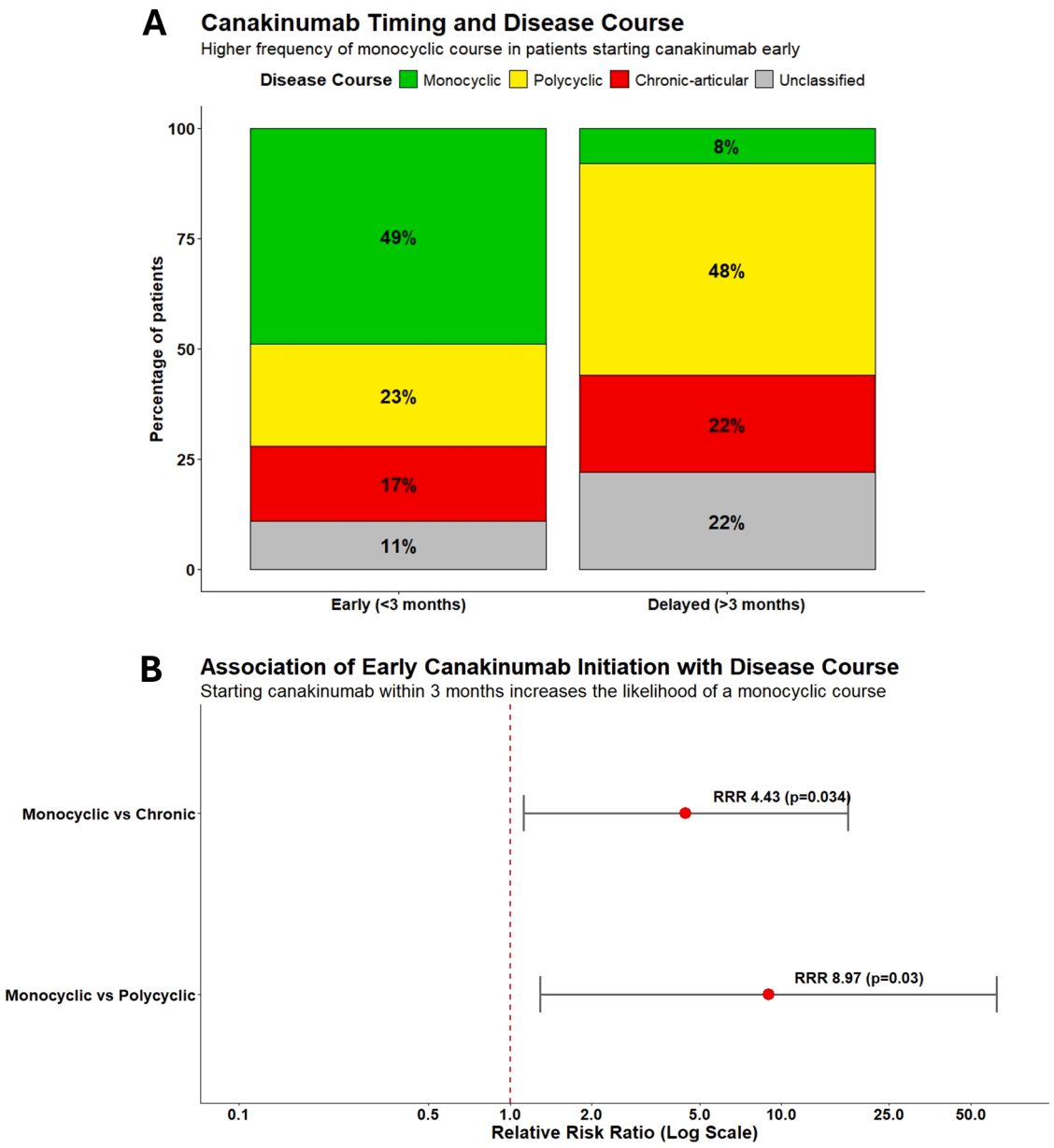

Fig. 5. Different types of disease course based on different canakinumab initiation timing and association of early canakinumab introduction with the monocyclic course. (A) Number of patients classified as having a monocyclic, polycyclic, or chronic-articular disease course among those treated with canakinumab ≤3 months versus >3 months from disease onset. Patients not yet classified are also reported. (B) Results from multinomial regression analysis showing the relative risk ratio (RRR) of being classified as monocyclic versus polycyclic or chronic-articular course when canakinumab was initiated within 3 months from disease onset, compared with later initiation.

on the timing of IL-1 inhibition initiation [7]. Nevertheless, our findings also highlight potential advantages associated with early use of canakinumab, supporting the hypothesis of a potential therapeutic window of opportunity. In particular, initiation of canakinumab within the first three months from disease onset was associated with long-term remission followed by treatment discontinuation. This finding may reflect greater stability of the complete clinical and laboratory response in patients treated with IL-1 inhibition early, an interpretation further supported by the reduced need for concomitant cDMARDs used to sustain the efficacy of IL-1 inhibition. In this cohort, the association between late initiation of canakinumab and the need for concomitant cDMARDs did not reach statistical significance, likely due to the limited sample size. Nonetheless, the observation that all patients requiring cDMARDs belonged to the group starting canakinumab beyond three months from disease onset is suggestive and may warrant further investigation in larger, adequately powered studies. Further studies will therefore be needed to clarify this issue.

Another relevant aspect emerging from the association between early canakinumab initiation and the ability to discontinue treatment in long-term remission concerns its potential impact on disease course. Specifically, early IL-1 inhibition may be associated with a monocyclic disease pattern rather than a chronic articular or polycyclic course. This finding is consistent with the hypothesis that early targeting of key inflammatory pathways through IL-1 blockade may positively influence long term disease trajectories. It should be specified that follow-up duration differed between groups, with shorter follow-up in the early-treatment group reflecting the more recent adoption of early IL-1 inhibition in clinical practice [15]. This may have limited the ability to fully capture the long-term disease course in some patients and may have resulted in provisional classification. In addition, such a clinically

meaningful concept requires long-term post-discontinuation follow-up, and only future data will determine whether this hypothesis is confirmed among patients who discontinued canakinumab due to sustained remission. It should also be acknowledged that disease course classification is inherently time-dependent, particularly for the monocyclic phenotype, which requires a sufficiently long period of observation without recurrence to be reliably defined. Conversely, in patients with prolonged disease duration, typically exceeding 12 months, the disease course is, by definition, more likely to be classified as polycyclic or chronic-articular. Therefore, differences in follow-up duration and in disease duration at the time of canakinumab initiation between groups may have influenced disease course categorisation. In particular, shorter follow-up in the early-treatment group, reflecting the more recent adoption of early IL-1 inhibition, may have led to provisional classification in some patients, while longer disease duration prior to canakinumab initiation in the late-treatment group increases the likelihood of observing recurrent flares. Although multivariable models were adjusted for disease course, such adjustment cannot fully account for the dynamic nature of disease evolution over time or for differences in observation windows between groups. Despite these limitations, initiation of canakinumab within three months from disease onset was more frequently observed in patients with a monocyclic disease course than in those with chronic-articular or polycyclic patterns, further supporting the potential prognostic benefit of early IL-1 inhibition.

An important alternative explanation that deserves explicit consideration is reverse causation in relation to the observed frequency of monocyclic disease course. Patients with an inherently monocyclic and self-limited disease phenotype might present with a more acute clinical onset [17], leading to earlier referral, earlier initiation of canakinumab, and a higher likelihood of favourable outcomes irrespective of treatment timing itself. In this scenario, the observed association between early IL-1 inhibition and improved long-term outcomes, including treatment discontinuation and monocyclic disease course, may at least in part reflect underlying disease biology rather than a causal effect of earlier treatment initiation. Although multivariable analyses were performed to account for measured confounders, residual confounding by indication and disease severity cannot be excluded in this observational setting, thereby limiting causal inference.

An additional key finding of this study is the greater ability to reduce and discontinue glucocorticoid therapy in patients treated early with canakinumab. In particular, patients initiating canakinumab within three months exhibited a significantly greater mean reduction in glucocorticoid dose, approximately 17.5 mg more than those treated later. This effect is only partially explained by higher initial glucocorticoid doses in the early-treatment group, likely reflecting a more acute disease phase. Indeed, although baseline glucocorticoid doses tended to be higher in patients starting canakinumab early, this difference was not statistically significant when compared with patients starting later. Moreover, the linear regression analysis confirming greater steroid-sparing effects in the early-treatment group was adjusted for baseline daily glucocorticoid dose. Interestingly, differences between groups tended to diminish at the last follow-up assessment. Consistently, the proportion of patients able to completely discontinue glucocorticoids was significantly higher in the early- canakinumab group at three and six months, whereas this difference disappeared at twelve months and at the last available evaluation. Overall, these findings suggest that during the first 3-6 months of treatment, early IL-1 inhibition allows for faster glucocorticoid tapering and discontinuation, while differences between early and late treatment initiation become less pronounced over time, likely reflecting a slower but ultimately comparable efficacy in patients treated later, as previously demonstrated for anakinra [6].

Taken together, these results indicate that early initiation of canakinumab may facilitate adherence to current EULAR/PReS recommendations for SD, which advocate for a marked reduction in glucocorticoid dosage within three months and, whenever possible, complete discontinuation by six months [15]. However, it is important to emphasise that, although the data presented in this study are of clinical interest, the implementation of early IL-1 inhibition in routine clinical practice is not without challenges. In the early phases of SD, diagnostic uncertainty is common, as the clinical presentation may overlap with infectious, malignant, and other inflammatory conditions, often requiring longitudinal follow-up before a definitive diagnosis can be established [18]. In addition, access to biotechnological therapies such as canakinumab is frequently influenced by regulatory and reimbursement pathways, which may delay treatment initiation even after the diagnosis has been confirmed. These factors, together with the need for careful differential diagnosis and patient-tailored treatment escalation strategies, may partly explain why early IL-1 blockade is not consistently implemented in real-world practice, despite its potential benefits.

Notably, early IL-1 blockade was not restricted to patients initiating canakinumab within three months, as 5 patients in the early-treatment group and 23 patients in the late-treatment group had received anakinra prior to canakinumab administration. However, anakinra had been administered at a fixed dose of 100 mg/day in all adult patients included in this study, as it was considered a likely suboptimal regimen toward adequate IL-1 inhibition. Accordingly, these patients subsequently required switch to canakinumab as a more effective IL-1-targeted therapy. This rationale also underlies the study design, which focused on patients treated with on-label canakinumab rather than anakinra, in order to reduce the potential bias associated with underdosing and consequently inadequate IL-1 inhibition. Indeed, in adult patients with Still's disease, the on-label dosing of anakinra is 100 mg/day regardless of body weight, whereas canakinumab is administered at 4 mg/kg every 4 weeks, up to a maximum of 300 mg every 4 weeks.

This study has limitations, including its observational design, which precludes causal inference and may be affected by residual confounding despite multivariable adjustment. The small proportion of patients initiating canakinumab within three months may have limited power for some outcomes, particularly cDMARD use. Given the sample size imbalance between the early (n=35) and late (n=155) treatment groups, the study provides adequate precision to detect moderate-to-large differences between groups, whereas smaller effect sizes may not be reliably detected. This is reflected in the width of confidence intervals for several outcomes. Therefore, findings should be interpreted in terms of effect size estimates and their precision rather than statistical significance alone. Heterogeneous follow-up after treatment discontinuation limits conclusions on long-term disease remission. The three-month cut-off, although clinically reasonable, is partly arbitrary. Noteworthy, additional residual confounding may be present due to unmeasured variables, including prior treatment exposure, temporal changes in therapeutic strategies, and centre-level effects, which could not be formally accounted for due to sample size constraints and the multicentre structure of the registry. In particular, the comparison between early and late treatment groups inherently reflects differences in prior treatment exposure and disease stage, which may have influenced both treatment decisions and outcomes. However, despite the more acute disease presentation in patients treated early, no clear signal of worse outcomes was observed in this group. We also acknowledge that multiple endpoints were assessed without adjustment for multiplicity. This reflects the exploratory nature of the study within a real-world registry framework. Therefore, the risk of type I error should be considered when interpreting statistically significant findings, particularly those with borderline p values, and results should be regarded as hypothesis-generating. Missing data varied across time points and reflect the real-world nature of registry-based data collection. Although analyses were conducted on available cases, the possibility of informative missingness cannot be excluded. It is noteworthy that follow-up duration differed between groups, with shorter follow-up in the early-treatment group reflecting more recent treatment practices. This may have limited the ability to fully capture long-term outcomes, including disease course classification and treatment discontinuation, and may have led to provisional classification in some patients. Nevertheless, despite the study

limitations, the large real-world cohort and consistent patterns across outcomes provide supportive evidence for the clinical relevance of early IL-1 inhibition in SD.

In conclusion, canakinumab is highly effective in SD regardless of the timing of treatment initiation in relation to disease onset. However, early initiation may be associated with treatment discontinuation due to long-term remission and appears to be linked to a greater frequency of a monocyclic disease course. Moreover, early treatment improves the ability to reduce and discontinue glucocorticoids in the short term. Future studies are warranted to clarify whether later initiation of canakinumab is more frequently associated with the need for concomitant cDMARD therapy.

Ethics approval and consent to participate

The Ethics Committee of Azienda Ospedaliero-Universitaria Senese, Siena, Italy (Ref. N. 14951; NCT05200715) approved the study, which was performed according to the Good Clinical Practice guidelines and the latest Declaration of Helsinki. Written informed consents for involved patients were collected. Clinical data are kept in accordance with the EU General Data Protection Regulations (GDPR), or other counterparts, on the processing of personal data and the protection of privacy (2016/679/EU).

Funding

The author(s) declare no financial support was received for the reseach, autorship, and/or publication of this article.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. Requests to access these datasets should be directed to the corresponding author: Luca Cantarini, MD, PhD, Research Center of Systemic Autoinflammatory Diseases and Behçet's Disease Clinics, Department of Medical Sciences, Surgery and Neurosciences, University of Siena.

Author contributions

All the authors substantially contributed to the conception or design of the work, the acquisition and interpretation of data and critically revised the paper. All the authors approved the final version and agreed to be responsible for all the aspects of the work. In addition, AV wrote the first draft of the manuscript and performed the preliminary data analysis and interpretation. VC, JS, GL, AT, GR, PPS, LD, EDB, SO, FB, FM, SB, MF, PR, AC, IYC, EKK, KL, HCE, RP, JC, LDS, CF, PC, FLT, MCM, SAAM, LF, DR, EV, GG, LLB, MP, GE, RG, GC, PS, EB, RG, PB, ANO, AA, ALG, HD, FAO, AK, MP, AE, FG, PP, FC, CC, JHR, GH, CB, IAA, ARM, AGG, CG, ADP, MET, ALB, EF, FTR, BS, BO, MT, AC, VP, OB, TK, MG, AI, MSC, AM, EDG, FC, SE, ST, MTH, EWS, JTR, EMN, AB, CF, BF, AHA, OK, LC were involved in the study according to their active role in enrolling patients in the AIDA Network Registries; AB, is also the bioengineer involved in the technical management of the platform and registries; LC took care of the final revision of the manuscript and accounted for AIDA Registries Coordinator.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This research is supported (not financially) by the European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA). of the authors of this publication [Antonio Vitale, Valeria Caggiano, Jessica Sbalchiero, Carla Gaggiano, Annachiara Alemanno, Francesco Gavioli, Alberto Balistreri, Bruno Frediani, Claudia Fabiani and Luca Cantarini; José Hernández-Rodríguez; Micol Frassi and Francesca Crisafulli; Petros P. Sfikakis and Katerina Laskari; Paolo Sfriso; Serena Bugatti and Ludovico De Stefano] belong to institutes that are members of the ERN RITA [Azienda Ospedaliero-Universitaria Senese of Siena; Hospital Clínic of Barcelona; Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia; Laiko General Hospital of Athens; Azienda Ospedale-Università Padova; Fondazione I.R.C.C.S. Policlino San Matteo].

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2026.153030.

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