本製造販売承認事項一部変更承認申請の臨床データパッケージに含まれる試験は，国内第 II 相試験（IACT21071 試験）のみであり，臨床的有効性の内容は「2.5 臨床に関する概括評価」と重複するため，これを参照することとした。

本製造販売承認事項一部変更承認申請の臨床データパッケージに含まれる試験は，国内第 II 相試験（IACT21071 試験）のみであり，臨床的安全性の内容は「2.5 臨床に関する概括評価」と重複するため，これを参照することとした。

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1 生物薬剤学試験

該当なし

2 臨床薬物動態（PK）試験

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3 臨床薬力学（PD）試験

該当なし

4 有効性及び安全性試験

4.1 申請する適応症に関する比較対照試験

該当なし

4.2 非対照試験

4.2.1 IACT21071 試験

第 5 部に添付する IACT21071 試験 CSR の 2 章概要に示す。

4.3 その他の臨床試験

該当なし

5 公表論文情報

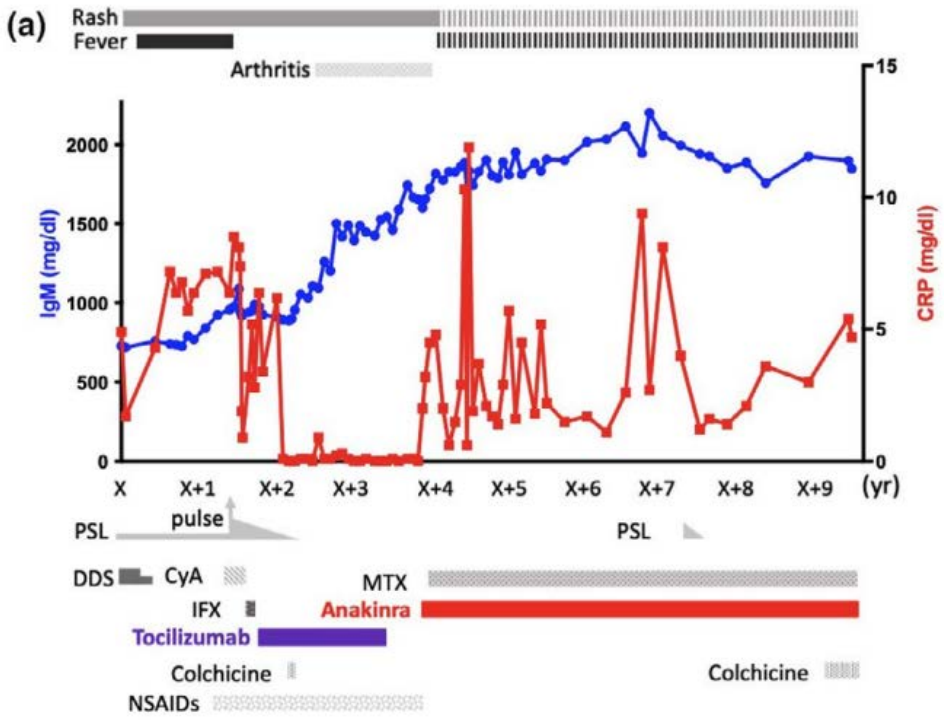
IACT21071 試験でのカナキヌマブの 8 週間ごとの投与による低疾患活動性の持続と比較するため，未治療又はステロイド等の対症療法的に行われる治療（以下，既存治療）下で約 1 年以上の臨床経過の詳細が報告された症例報告を抽出した。これらの報告内容は，以下の 2 つの抽出方法別にそれぞれ 5.1 項及び 5.2 項に示し，公表文献は「5.4 参考文献」に添付する。

1. 国内症例情報
   Takimoto-Ito ら（2023）による国内シュニッツラー症候群患者 36 名を報告した公表文献での引用に基づき特定した 33 名分の症例報告から抽出した。
2. 国内外公表文献情報
   2014 年 9 月から 2024 年 10 月の公表文献を「Schnitzler syndrome」又は「Schnitzler’s syndrome」を検索語として PubMed 検索し，特定した国内外シュニッツラー症候群患者の症例報告から抽出した。

5.1 国内症例情報

Takimoto-Ito ら（2023）による国内シュニッツラー症候群患者 36 名を報告した公表文献での引用に基づき特定した 33 名分の症例報告のうち，未治療又は既存治療による対症療法下での約 1 年以上の臨床経過の詳細が報告された公表文献は 4 報（7 名）であった。これらの公表文献の報告内容を以下に示す。なお，臨床経過図は公表文献内に提示された図を示し，提示がない場合は報告内容に基づき作図した。

Table 5-1 Takimoto-Ito et al. 2021，Case 1

公表文献	Takimoto-Ito R, Kambe N, Kogame T, et al. (2021) Refractory serum immunoglobulin M elevation during anti-interleukin (IL)-1- or IL-6-targeted treatment in four patients with Schnitzler syndrome. J Dermatol; 48(11):1789-92.
年齢/性別	63/女
罹患期間	1.5 年
初期症状	A few months later, she developed intermittent fever and manifested recurrent urticarial rash.
臨床経過	• There was a partial response to oral prednisolone (20 mg/day) and diaphenylsulfone (75 mg/day), but erythema flared after prednisolone was tapered. • She was unresponsive to cyclosporin or infliximab. • Tocilizumab resolved urticarial rash within 24 h of the first injection, but the effect gradually subsided and she developed arthritis. • We switched the treatment to anakinra, which dramatically reduced the skin eruption and other clinical symptoms, including abnormal laboratory findings. • Of note, case 1 still exhibited recurrent fever with elevated CRP levels during anakinra therapy, but it is worth noting that the daily injections were difficult due to high cost and pain at the injection site. 

未治療又は既存治療での臨床症状まとめ	患者は間欠性の発熱及び再発性の蕁麻疹様発疹を有した。1 年以上のプレドニゾロン等の投与で部分寛解が得られたが，プレドニゾロンの漸減により紅斑は再燃した。シクロスポリンやインフリキシマブの投与で効果はみられなかった。なお，アナキンラ療法中も CRP 値の上昇を伴う再発性の発熱がみられるが，これは注射部位の痛みとアナキンラを自己輸入しているための高コストのため，毎日の注射は困難であったことによる。

Table 5-2 Takimoto-Ito et al. 2021, Case 2

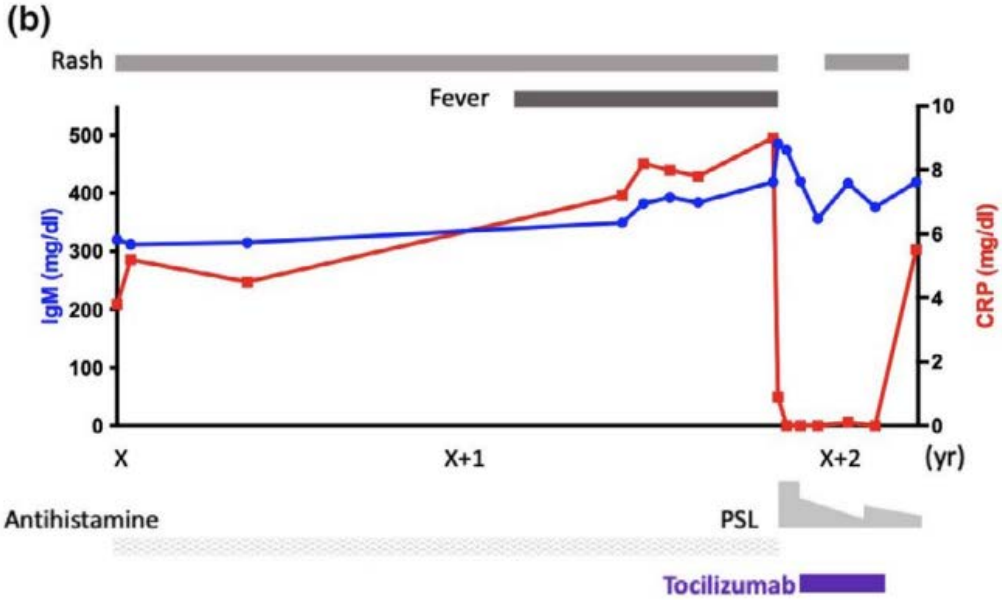
公表文献	Takimoto-Ito R, Kambe N, Kogame T, et al. (2021) Refractory serum immunoglobulin M elevation during anti-interleukin (IL)-1- or IL-6-targeted treatment in four patients with Schnitzler syndrome. J Dermatol; 48(11):1789-92.
年齢/性別	65/男
罹患期間	3 年
初期症状	On admission, he had pruritic edematous erythema on his trunk and reticular erythema on his legs.
臨床経過	• Several antihistamines were administrated but were ineffective. Eighteen months after his first visit, he developed a fever to 38°C with a duration of 4-5 days every 2 weeks. • We administrated oral prednisolone (30 mg/day) and tocilizumab, which dramatically reduced the skin eruption and other clinical symptoms, except for the IgM monoclonal gammopathy (419 mg/dL). He discontinued tocilizumab against medical advice, but when the symptoms recurred, he restarted the tocilizumab. 
未治療又は既存治療での臨床症状まとめ	患者は体幹に掻痒性浮腫性紅斑，下肢に網状紅斑が認められた。複数の抗ヒスタミン薬を 1 年以上投与したが，効果はなかった。初診から 18 ヵ月後には 4～5 日間持続する 38°C の発熱が 2 週ごとに発現するようになっていた。

Table 5-3 Takimoto-Ito et al. 2021, Case 3

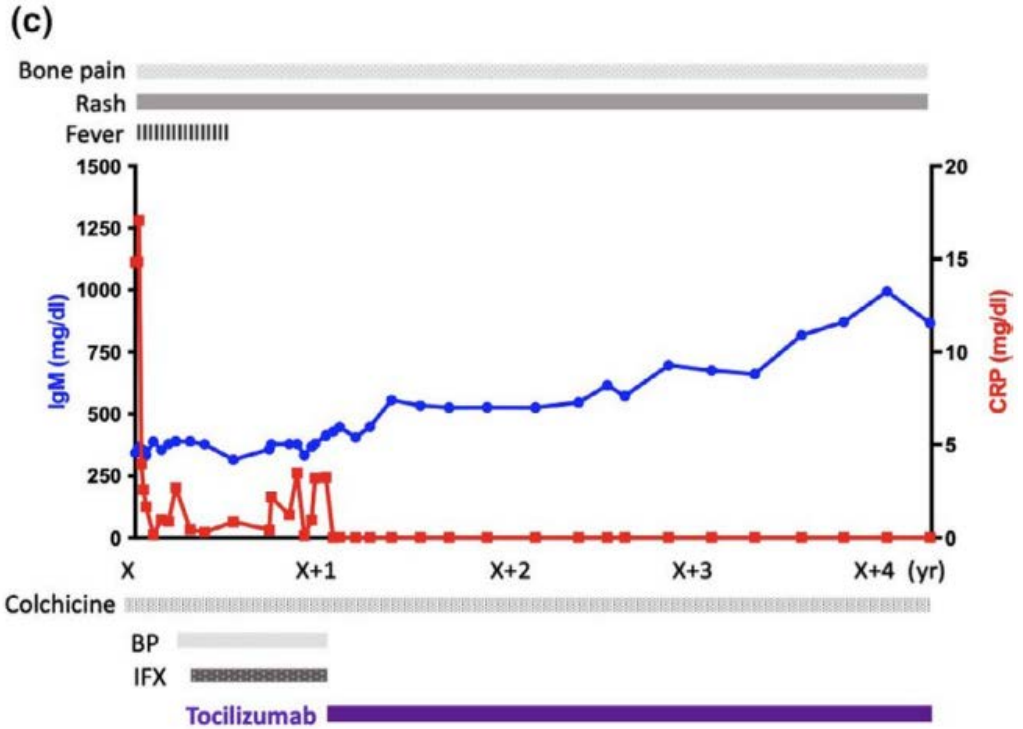
公表文献	Takimoto-Ito R, Kambe N, Kogame T, et al. (2021) Refractory serum immunoglobulin M elevation during anti-interleukin (IL)-1- or IL-6-targeted treatment in four patients with Schnitzler syndrome. J Dermatol; 48(11):1789-92.
年齢/性別	43/女
罹患期間	Not reported
初期症状	She initially sought evaluation by another physician for recurrent fever, extremity pain, and skin rash when she was 43 years old.
臨床経過	• The effect of non-steroidal anti-inflammatory drugs, bisphosphonate, and colchicine was limited. • Infliximab failed to resolve the symptoms. • Tocilizumab, however, was effective in reducing bone pain, but the rash persisted. After several years, she had an osteomyelitis recurrence and the serum IgM level increased (866 mg/dL). 
未治療又は既存治療での臨床症状まとめ	患者は骨痛，皮疹，及び再発性の発熱を有した。1 年以上のコルヒチン等の投与による効果は限定的であり，約半年後に発熱は消失したが，骨痛及び皮疹は持続した。インフリキシマブは無効であった。

Table 5-4 Takimoto-Ito et al. 2021, Case 4

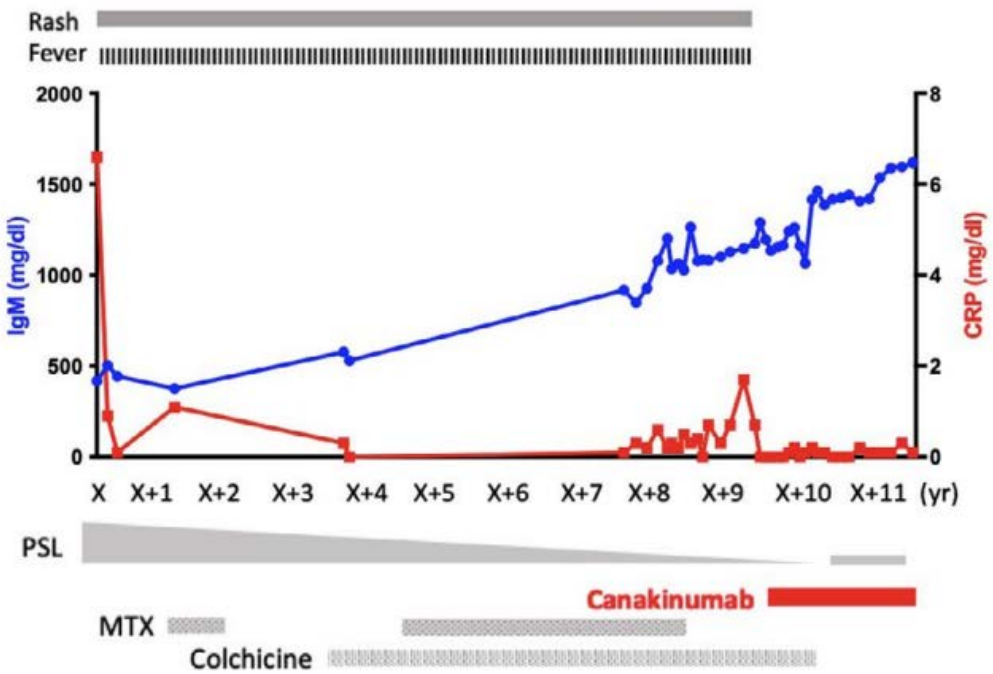
公表文献	Takimoto-Ito R, Kambe N, Kogame T, et al. (2021) Refractory serum immunoglobulin M elevation during anti-interleukin (IL)-1- or IL-6-targeted treatment in four patients with Schnitzler syndrome. J Dermatol; 48(11):1789-92.
年齢/性別	63/女
罹患期間	7 年
初期症状	A 63-year-old woman was referred to our hospital with recurrent fever to 39°C, leg pain, and urticaria.
臨床経過	• Prednisolone (15 mg/day), methotrexate, and colchicine were partially effective. • Canakinumab dramatically reduced the symptoms and abnormal laboratory findings, except for IgM monoclonal gammopathy (1597 mg/dL). (d) 
未治療又は既存治療での臨床症状まとめ	患者は 39°C の再発性の発熱，下肢痛，及び皮疹を有した。プレドニゾロン等の投与による効果は部分的であり，再発性の発熱及び皮疹は 9 年以上持続した。

Table 5-5 Shirabe et al. 2001

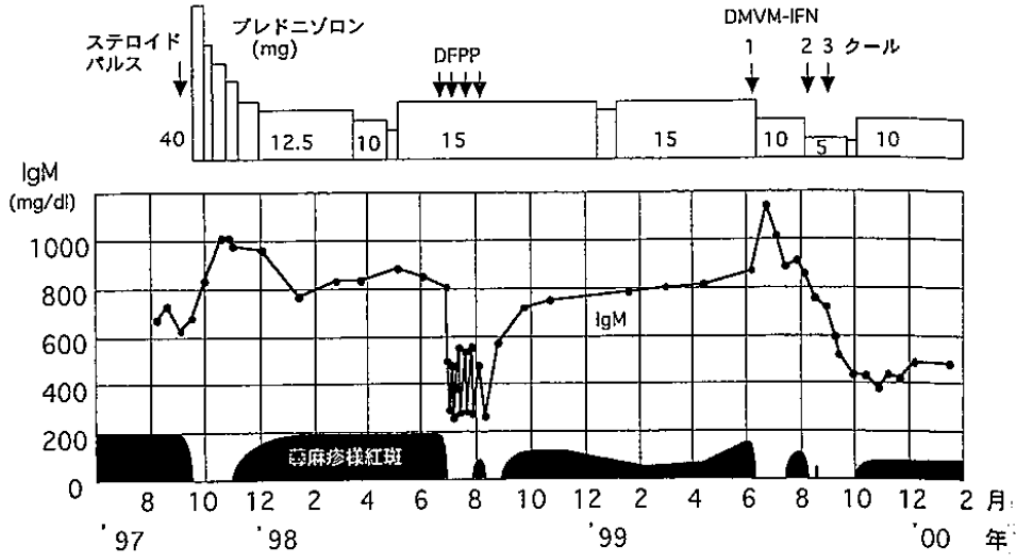
公表文献	Shirabe H, Hino N, Fujimoto M, et al. (2001) A case of Schnitzler's syndrome. Nihon Hifuka Gakkai Zasshi; 111:947-53.
年齢/性別	46/男
罹患期間	Not reported
初期症状	全身の蕁麻疹様紅斑，発熱，リンパ節腫脹を生じ，血液検査にて IgM-κ型 M 蛋白が確認された。骨髄穿刺，リンパ節生検，その他全身検索にて悪性所見はみられず，シュニッツラー症候群と診断。
臨床経過	非ステロイド消炎薬，抗ヒスタミン薬にて症状の改善がみられずステロイドパルス療法を行った。パルス療法終了後，皮疹，発熱，リンパ節腫脹は劇的に改善した。その後内服ステロイド減量にて症状の再燃がみられた。次に二重膜濾過血漿交換療法を施行した。血漿交換直後 2～3 日で皮疹は改善したが，治療頻度を週 2 回から 1 回に変えると再燃した。血清 IgM 値と皮疹の程度には相関がみられなかった。その後ステロイド減量にて発熱，皮疹の再燃がみられたため，化学療法（DMVM-IFNα 療法）を 3 クール行った。皮疹は改善したが終了後に軽度の再燃がみられた。血清 IgM 値は化学療法終了 5 ヵ月後の時点でコントロールされ，ステロイド治療後は発熱もみられていない。  図 3 初診後の経過
未治療又は既存治療での臨床症状まとめ	患者は全身の蕁麻疹様紅斑，発熱，及びリンパ節腫脹を有した。1 年以上のプレドニゾロン等の投与により，皮疹，発熱，及びリンパ節腫脹は軽減又は消失が認められたが，治療薬の減量や投与間隔延長により再発や悪化を繰り返した。DMVM-INFα 療法を 3 クール行った後 5 ヵ月間，発熱は認められなかったが，蕁麻疹様紅斑は軽減したものの再燃を繰り返した。

Table 5-6 Morita et al. 1995

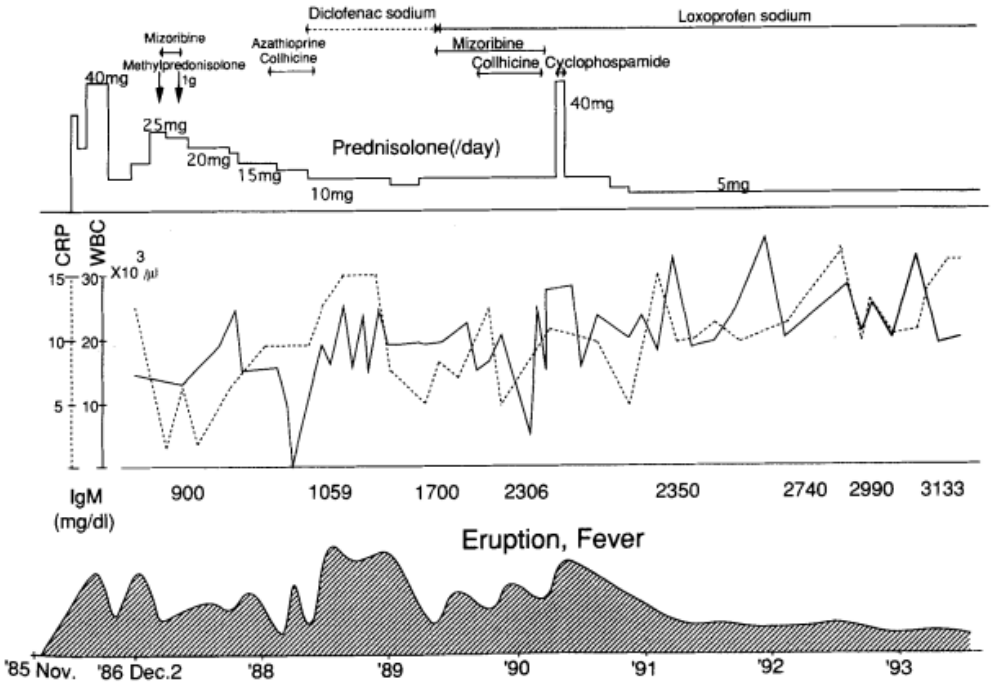
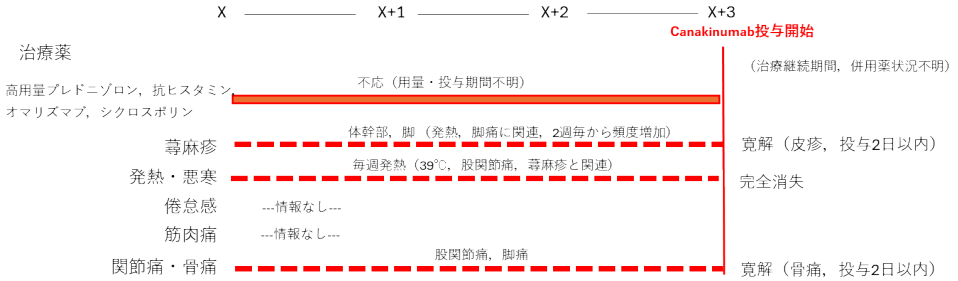
公表文献	Morita A, Sakakibara S, Yokota M, et al. (1995) A case of urticarial vasculitis associated with macroglobulinemia (Schnitzler's syndrome). J Dermatol; 22(1):32-5.
年齢/性別	50/女
罹患期間	10 年
初期症状	In November of 1985, a 42-year-old Japanese woman first noted urticaria-like eruptions on the trunk; since then, she has continued to develop such lesions on her limbs. The eruptions have been accompanied by recurrent fever, arthralgia, myalgia, general fatigue and weight loss.
臨床経過	• Prednisolone and pulse therapy of methylprednisolone were ineffective in treating the cutaneous lesions. • Immunosuppressive agents and colchicine were also tried without success. • A nonsteroidal anti-inflammatory drug was effective for controlling the fever. Serum IgM concentration and white blood cell count have gradually increased with time. • For the last several years, small doses of prednisolone and an anti-inflammatory drug (Loxoprofen sodium), administered on the appearance of preceeding symptoms just before fever, such as skin pain, arthralgia and chills, have allowed partial control of the intensity and extent of the urticaria, as well as myalgia and arthralgia. The duration of eruptions has become shorter than 24 hours.  Fig. 3. Clinical course.
未治療又は既存治療での臨床症状まとめ	患者は体幹や四肢に蕁麻疹様皮疹が認められた。皮疹は再発性の発熱，関節痛，全身性の筋肉痛，及び体重減少を伴った。8 年以上のプレドニゾロン等の投与により，皮疹や発熱は軽減と悪化を繰り返しながら持続した。過去数年は，皮膚疼痛，関節痛，又は悪寒といった発熱前の先行症状の発現時に，少量のプレドニゾロン等を投与することで，蕁麻疹の重症度及び範囲，並びに筋肉痛及び関節痛を部分的にコントロールすることができ，皮疹の持続は 24 時間未満となった。

Table 5-7 Fujita et al. 2021

公表文献	Fujita Y, Asano T, Sakai A, et al. (2021) A case of Schnitzler's syndrome without monoclonal gammopathy successfully treated with canakinumab. BMC Musculoskelet Disord; 22(1):257.
年齢/性別	43/女
罹患期間	4 年
初期症状	A 43-year-old female was referred to our department for evaluation of recurrent febrile attack for 3–4 days, leg pain, and urticarial eruption.
臨床経過	• Three years before the visit, a weekly febrile attack of > 39°C that lasted 3-4 days. Her symptoms started with urticarial rash in the trunk and legs associated with high fever and progressing leg pains. The urticarial rash initially occurred once every 2 weeks but gradually increased in frequencies. • Laboratory findings showed leukocytosis (11,900/μL) and elevated C-reactive protein levels (6.18 mg/dL) and serum amyloid A (SAA, 32.5 μg/mL). Markers for autoimmune diseases, including an anti-nuclear antibody and anti-neutrophil cytoplasmic antibody were negative. There was no M protein in immunoelectrophoresis. • The patient had been treated with high-dose prednisolone, antihistamines, omarizumab, and cyclosporine A; however, she was unresponsive to these various treatments. • Skin rash and bone pain were resolved within 2 days of the first injection of canakinumab. Inflammatory markers, such as CRP and SAA, were normalized after 7 days from the first injection. The patient noticed significant improvement and recurrent febrile attack completely disappeared. 
未治療又は既存治療での臨床症状まとめ	患者は 3 年間，39 度を超える発熱発作が週に 3～4 日持続し，発熱発作は股関節痛及び蕁麻疹様皮疹を伴い，解熱後も回復しなかった。蕁麻疹様発疹は下肢痛の進行を伴う体幹及び下肢に起こり，2 週間に 1 回から徐々に発現頻度が増加した。高用量プレドニゾロン，抗ヒスタミン薬，オマリズマブ，シクロスポリン A による治療を受けていたが，これらさまざまな治療に反応しなかった。

5.2 国内外公表文献情報

2014 年 9 月から 2024 年 10 月の公表文献を「Schnitzler syndrome」又は「Schnitzler's syndrome」を検索語として PubMed 検索し，特定した国内外シュニッツラー症候群患者の症例報告のうち，未治療又は既存治療による対症療法下での約 1 年以上の臨床経過の詳細が報告された公表文献は 10 報であった。これらの公表文献うち，5.1 項に示した公表文献 2 報を除く，8 報（8 名）の報告内容を以下に示す。なお，臨床経過図は公表文献内に提示された図を示し，提示がない場合は報告内容に基づき作図した。

Table 5-8 Wesselmann et al. 2023

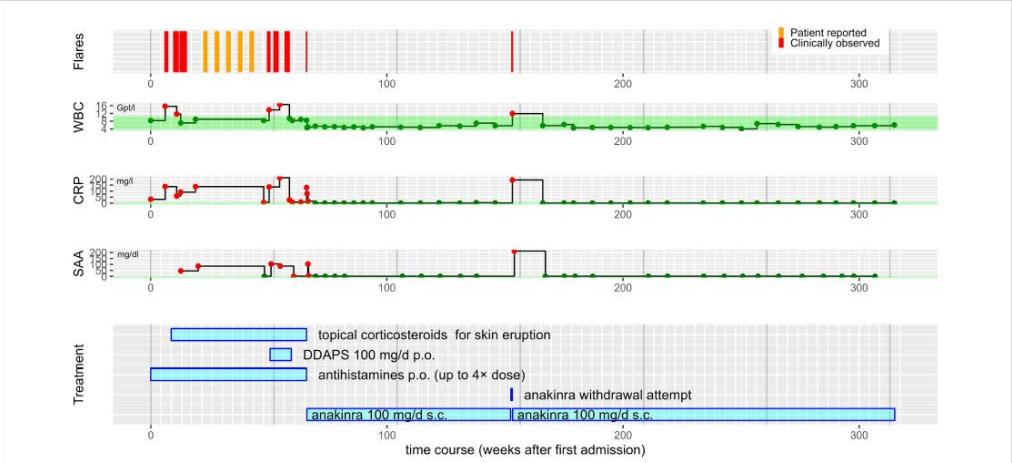
公表文献	Wesselmann AS, Künstner A, Fähnrich A, et al. (2023) Case report: Schnitzler-like syndrome without monoclonal gammopathy. Front Immunol; 14:1166620.
年齢/性別	75/男
罹患期間	12 ヵ月
初期症状	A 75-year-old man presented to our department with recurrent non-pruritic, not painful, annular urticarial plaques on the extremities and the trunk for 12 months. The inflammatory episodes lasted for 7-10 days without severe general impairment, arthralgia or fever.
臨床経過	• Neither high-dose antihistaminics (cetirizine 10 mg or desloratadine 5 mg up to 4 × daily) over six months nor dapsone (100 mg/day) for three months effectively prevented the relapse of inflammatory episodes. • Within five hours of anakinra administration, the urticarial plaques resolved entirely. The patient has remained in remission under continued treatment with anakinra 100 mg/day during follow-up for more than four years. • Temporary discontinuation of anakinra for two days resulted in a relapse with re-emergence of cutaneous urticarial plaques accompanied by fever, joint pain, and elevated inflammatory markers.  FIGURE 2 Overview of the patient's disease course. Step plots of laboratory parameters over time aligned with bar chart of treatment modalities. With the exception of an immediate relapse during a single anakinra withdrawal attempt, the patient has remained free of inflammatory episodes for a follow period of about 250 weeks (~5 years) now. Different antihistamines including cetirizine 10 mg p.o were given up to 4x standard dose. Topical corticosteroids included methylprednisolone and clobetasol. WBC, white blood cell counts, in 1/nl. CRP, C-reactive protein concentration in mg/l. SAA, serum amyloid A concentration in mg/dl. The reference ranges are shaded in green. Red dots indicate values outside the reference range, dark green dots values within. The white vertical grid lines indicate months, the grey vertical grid lines years.
未治療又は既存治療での臨床症状まとめ	患者は受診時に四肢及び体幹に非掻痒性かつ非疼痛性の再発性の環状蕁麻疹様症状を有した。炎症症状は 7～10 日間持続し，重度の全身障害，関節痛，又は発熱はなかった。抗ヒスタミン薬等を 1 年以上投与したが，症状改善はみられず，約 50 週で 9 回の症状発現がみられた。

Table 5-9 Kano and Sugihara 2023

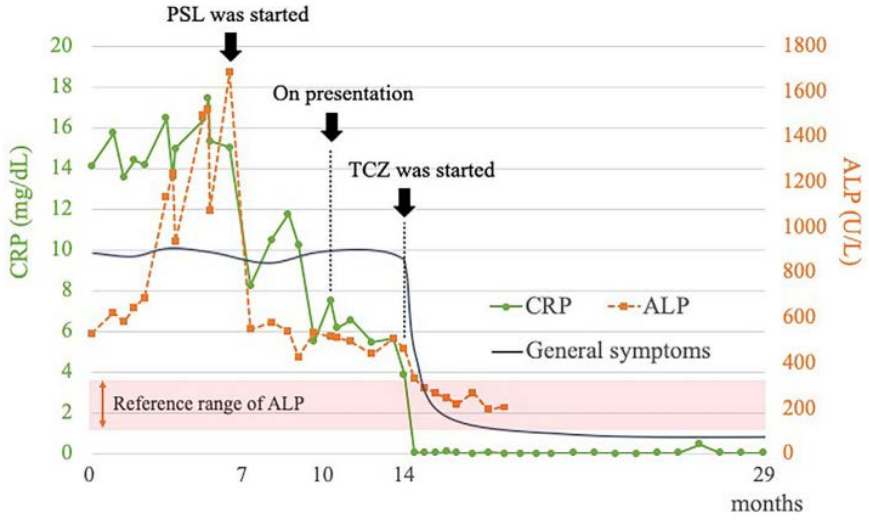
公表文献	Kano Y and Sugihara M (2023) Schnitzler Syndrome Presenting as a Fever of Unknown Origin with Elevated Alkaline Phosphatase Levels. Intern Med; 62(9):1361-4.
年齢/性別	60/男
罹患期間	19 ヵ月以上
初期症状	A 60-year-old man was referred to our hospital with a 1- year history of a fever, malaise, and chronic rash. The urticaria was slightly pruritic and mostly present on his trunk and limbs sparing the face, palms, and soles.
臨床経過	• The treatment failed to improve his symptoms despite a slight decrease in his C-reactive protein (CRP) and ALP levels. • Colchicine 1 mg/day was initially administered but had no effect. • The response to tocilizumab was very good, and the longstanding fever, malaise, and urticaria decreased several days after the start of the treatment. The CRP and ALP values also normalized. Remission was maintained with tocilizumab monotherapy for two years after the start of treatment, but IgG lambda monoclonal protein was still positive at two years after the initiation of tocilizumab therapy.  **Figure 1. Clinical course of the patient. CRP: C-reactive protein, ALP: alkaline phosphatase, PSL: prednisolone, TCZ: tocilizumab**
未治療又は既存治療での臨床症状まとめ	患者は発熱，倦怠感，及び慢性発疹を有した。蕁麻疹は軽度の掻痒性であり，大部分は体幹及び四肢に認められた。無治療又はプレドニゾロンあるいはコルヒチンを投与した 14 ヵ月間で臨床症状の改善はなかった。

Table 5-10 Puxkandl et al. 2023

公表文献	Puxkandl V, Currie A, Hoetzenecker W, et al. (2023) Therapy resistant urticaria as a long-term symptom of an incomplete Schnitzler syndrome. Allergy Asthma Clin Immunol; 19(1):64.
年齢/性別	58/男
罹患期間	8 年
初期症状	In December 2013, a 58-year-old man presented with daily recurring hives that covered almost the entire body, increasing in size in the groin area on both sides, sparing the face. The pruritus was mild to nonexistent.
臨床経過	**Table 3** Process of diagnosis

DATE	DIAGNOSIS	THERAPY	
12/2013	Intolerance reaction (ACE-Inhibitors)	Corticosteroids, AH	Hives covering the whole body
03/2014	Chronic spontaneous urticaria		
05/2014		AH	
08/2014		Omalizumab	
10/2014		AH	Augmented urticaria after meat consumption
06/2017			Urticaria pigmentosa (particularly trunk)
07/2017	Cutaneous mastocytosis—skin biopsy	AH, Corticosteroids (Azathioprin as MG therapy)	No local findings
04/2018	Cutaneous mastocytosis—bone marrow biopsy IgM MGUS DD CSU	AH	Augmented hives
05/2021		Omalizumab	Arthralgia and urticaria
11/2021		Omalizumab increased dose	Augmented hives
02/2022	Schnitzler syndrome	AH	Augmented hives after vaccination, recurring fever
03/2022		Anakinra	Recession of hives, reaction at injection site, Return of hives after therapy discontinuation
04/2022		Canakinumab	Complete remissions of symptoms

Not all appointments at the physician are displayed

ACE Angiotensin-converting enzyme, *AH* Antihistamines, *MG* Myasthenia gravis, *DD* Differential diagnosis, *CSU* chronic spontaneous urticaria

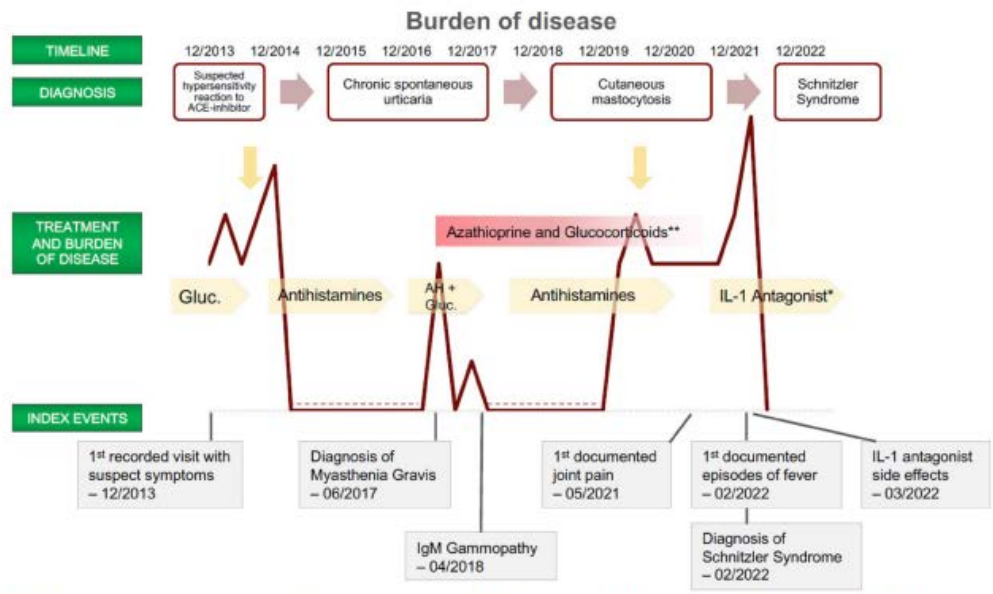


Fig. 1 Figurative representation of recorded burden of disease, treatments, and diagnosis over the time. *initially Anakinra, then (04/2022) Canakinumab, **Myasthenia Gravis treatment. Yellow arrows indicate Omalizumab therapy, dashed line indicates period without recorded hospital visit. ACE; Angiotensin-converting enzyme, AH; Antihistamines, Gluc.; Glucocortico

未治療又は既存治療での臨床症状まとめ	患者はほぼ全身を覆う再発性蕁麻疹を毎日呈した。掻痒は軽度又は伴わなかった。無治療又はステロイド等を投与した 8 年間，臨床症状は改善と悪化を繰り返し，新たに関節痛や再発性の発熱も発現した。

Table 5-11 Salcedo-Mingoarranz et al. 2023

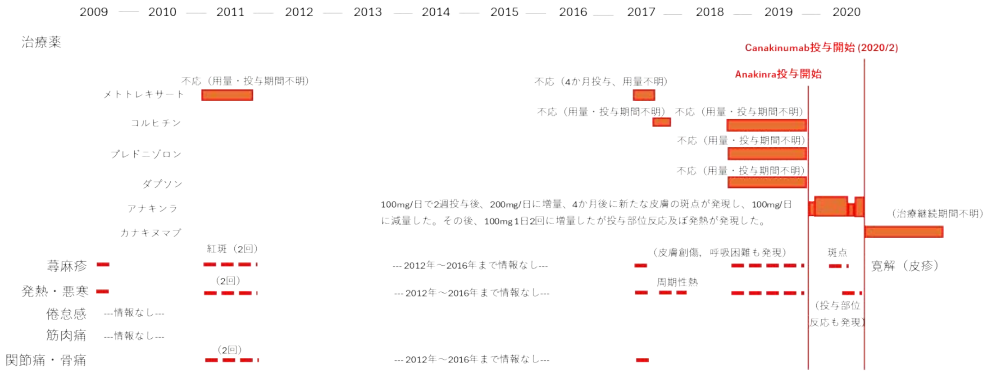
公表文献	Salcedo-Mingoarranz AL, Dorado-Fernández M, García-Martínez S, et al. (2023) Schnitzler syndrome refractory to anakinra: successful treatment with canakinumab. J Dermatolog Treat; 34(1):2242705.
年齢/性別	64/女
罹患期間	3 年以上
初期症状	A 64-year-old woman affected by skin rash and a monoclonal gammopathy of uncertain significance (small lambda IgG peak) was admitted in October 2009 with fever, severe rash, elevated CRP and dyspnea.
臨床経過	• In 2011, two episodes of fever, erythema and arthralgia were reported. Methotrexate was prescribed but without any clinical benefit. • In March 2017, the patient was admitted with fever, erythema and myalgia. • In June 2017, methotrexate was prescribed due to clinical suspicion of perichondritis and new facial edema episodes, nevertheless, four months later methotrexate was discontinued and colchicine was started since the patient developed periodic fever. • Between July 2018 and May 2019, the skin wounds extended from the eyelids and cheeks, where they were first noticed, to the abdominal and lumbar regions, accompanied by erythematous plaques, fever and dyspnea. Throughout these months, the patient received colchicine, prednisone and dapsone without remission of symptoms. • Treatment with anakinra 100 mg daily was initiated. However, two weeks later anakinra was increased to 200 mg daily due to another disease outbreak. After four months, the patient developed new skin plaques, thus the dose was reduced to initial prescription. As a result of a disease relapse in November 2019, dermatologists resumed anakinra to 100 mg twice daily, however, this dose induced new injection-site reactions and fever. • Considering the persistence of the symptoms, the failure of previous therapies and anakinra intolerance, in February 2020, canakinumab was prescribed (150 mg every 8 weeks). The skin wounds rapidly improved since the first dose of canakinumab. Throughout this therapy, the patient has not required associated treatments and no adverse events have been observed. 
未治療又は既存治療での臨床症状まとめ	患者は 2009 年，2011 年に蕁麻疹様紅斑，発熱，関節痛が報告され，メトトレキサートが処方されたが，臨床的ベネフィットはなかった。2017 年より，発熱，紅斑，及び筋肉痛のため入院し，メトトレキサートが処方されたが効果はなく，その後コルヒチン，プレドニゾロン，ダプソンが投与されたが症状の寛解には至らなかった。

Table 5-12 Aslam et al. 2021

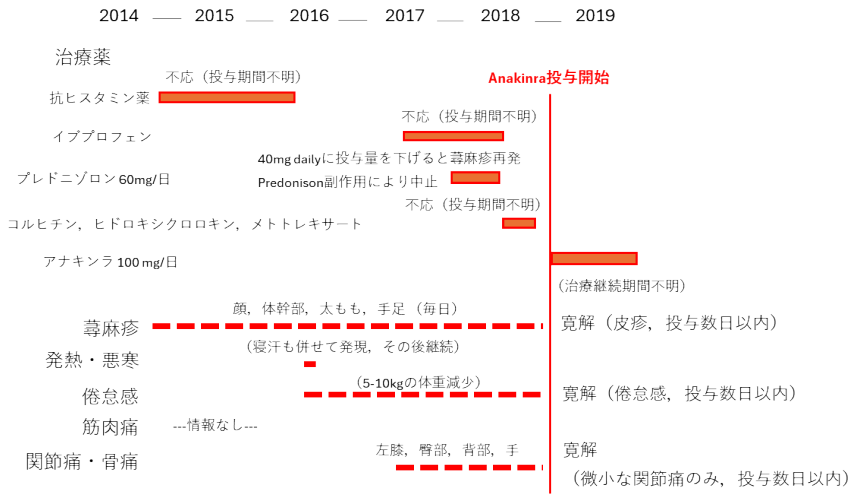
公表文献	Aslam F, Wiedmeier JE, DiCaudo DJ (2021) A Man With Recurrent Fever, Episodic Rash, and Pain. Arthritis Care Res (Hoboken); 73(8):1106-13.
年齢/性別	61/男
罹患期間	数年以上
初期症状	In November 2014, hives developed on his upper arms. Within weeks, the hives spread to his trunk and thighs but spared his face, palms, and soles. The symmetric, nonpruritic, nonpainful rash appeared without angioedema. The hives initially persisted for 5 days, followed by resolution for several days. This rash eventually progressed to being present the majority of the time. Each individual lesion, however, remained for less than 24 hours.
臨床経過	• In February 2016, the patient developed night sweats, which had not resolved by presentation at our clinic. On occasion the night sweats were drenching, and the patient slept on towels. He experienced fever and chills, with documented temperatures up to 102ºF. Fevers were episodic and without a fixed pattern. He reported constant fatigue. A 5-to 10-kg weight loss occurred but stabilized. • In June 2017, the patient developed unprovoked severe bone pain in the left leg just above the knee. The pain was unresponsive to ibuprofen. At times, he rated his pain as an 8 on a scale of 1 to 10 (10 being the worst). The patient then developed joint pain in his hips, back, and hands, without swelling or erythema. • His CRP level and ESR were moderately elevated. In addition, he had persistent leukocytosis. • Prednisone, 60 mg daily, was initiated. The prednisone resolved the urticarial rash but did not improve the joint pain or systemic symptoms. When prednisone was reduced to 40 mg daily, the hives recurred. The patient reported irritability as a side effect from the prescribed prednisone, and subsequently the medication was terminated. Treatment with colchicine, hydroxychloroquine, and methotrexate was unsuccessful. • Four years after symptom onset, the patient was frustrated with his undiagnosed, progressive condition and presented to our institution in October 2018. At presentation, he reported worsening hives, fatigue, and night sweats and persistent bone and joint pain most prominent in the left proximal tibia and distal femur. • The patient was started on anakinra, 100 mg daily. Within a few weeks, the patient had a remarkable response. His systemic symptoms, rash, and bone pain completely resolved, but only minimal joint pain from osteoarthritis. On a follow-up phone call at the time of this writing, the patient reported that he was doing very well on anakinra. 
未治療又は既存治療での臨床症状まとめ	患者は 2014 年より数年間持続する間欠性の発疹を呈した。2016 年に発熱し，体重減少を伴う持続的な倦怠感が認められた。2017 年に反復性の骨痛及び関節痛が発現した。抗ヒスタミン薬，グルココルチコイド，コルヒチン，ヒドロキシクロロキン，及びメトトレキサートによる治療が行われたが効果が認められなかった。

Table 5-13 Więsik-Szewczyk et al. 2020

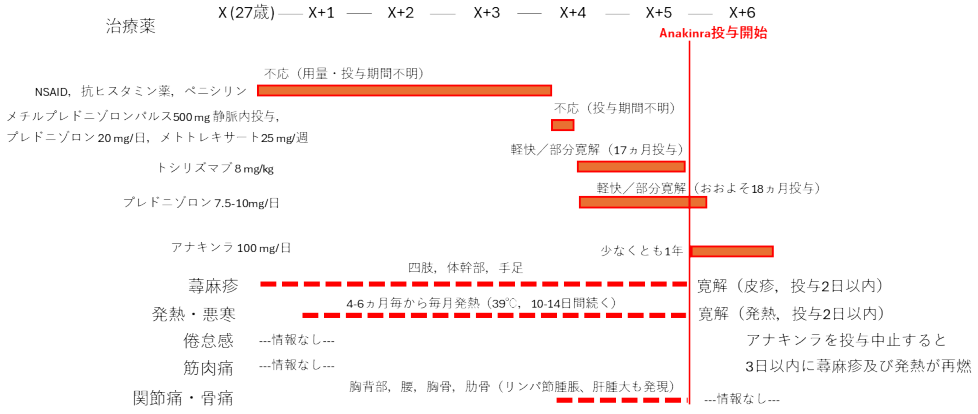
公表文献	Więsik-Szewczyk E, Felis-Giemza A, Dziuk M, et al. (2020) Schnitzler Syndrome in a 27-Year-Old Man: Diagnostic and Therapeutic Dilemma in Adult Auto-Inflammatory Syndromes A Case Report and Literature Review. Int J Gen Med; 13:713-9.
年齢/性別	32/男
罹患期間	5 年
初期症状	The patient was a 32-year-old Caucasian man with chronic urticaria since the age of 27.
臨床経過	• At the age of 28, it was accompanied by a recurrent fever of over 39 degrees, lasting for 10-14 days. The initial frequency of the fever attacks increased from once per 4-6 months to once every month. He was treated symptomatically with NSAID, antihistamine drugs and penicillin. • When he was 31, generalised lymphadenopathy, hepatomegaly, peripheral arthralgia occurred. Laboratory tests revealed leukocytosis 27x10^3/uL with neutrophilia (88%), CRP 14.2 mg/dL (0.1-1.0), monoclonal IgM antibody presence, ferritin 537.5 ng/mL (30-400). • He was diagnosed with adult onset Still's disease (AOSD) and received methylprednisolone pulses (500 mg intravenously for 3 consecutive days) followed by glucocorticoids (20 mg prednisolone orally once a day) and methotrexate (25 mg orally once a week), without any effect. • Then, tocilizumab (8 mg/kg intravenously once a month) was added with partial response: CRP lowered but the patient continued to complain about pain in thoracic back, hips, sternum and ribs and chronic urticaria. Low-grade fever up to 38 degrees regularly reappeared about one week before the tocilizumab infusions. In total the patient received seventeen doses of intravenous tocilizumab in combination with 7.5 to 10 mg daily of prednisolone. • On admission, his physical examination revealed peripheral lymphadenopathy and urticaria which covered his extremities, trunk, palms and soles. In his laboratory investigations leukocytosis with neutrophilia, CRP 3.1 mg/dL (ref 0-0.8), serum amyloid A (SAA) 24 mg/dL (ref < 0.64) were present. Serum IgG level was 347 mg/dL (ref. 700-1600), IgM 1110 mg/dL (40-230). • Anakinra 100 mg subcutaneously once a day was started. Urticaria and the fever disappeared within 2 days, SAA normalised within 4 weeks. Glucocorticoids were stopped within the first month of anakinra. An unintentional pause in the anakinra treatment caused the reoccurrence of high fever, and generalised urticaria within 3 days. During a continuous anakinra treatment, the patient remains in clinical remission. • After a one-year follow-up his SAA is stable within reference range, IgG is 792 mg/dL, IgM 907 g/dL (40-230). 
未治療又は既存治療での臨床症状まとめ	患者は 27 歳で慢性蕁麻疹を発現し，28 歳より 10～14 日間持続する 39 度超の反復性発熱を発現し，NSAIDs，抗ヒスタミン薬，及びペニシリンによる対症療法を受けた。31 歳より，全身リンパ節症，肝腫大，末梢関節痛が発現し，成人発症スチル病と診断され，メチルプレドニゾロンパルス，グルココルチコイド，及びメトトレキサートが投与されたが，効果はなかった。その後，トシリズマブが追加され部分寛解が得られたが，患者は胸背部，腰，胸骨，並びに肋骨の疼痛，及び慢性蕁麻疹を訴え続けた。

Table 5-14 Fank et al. 2018

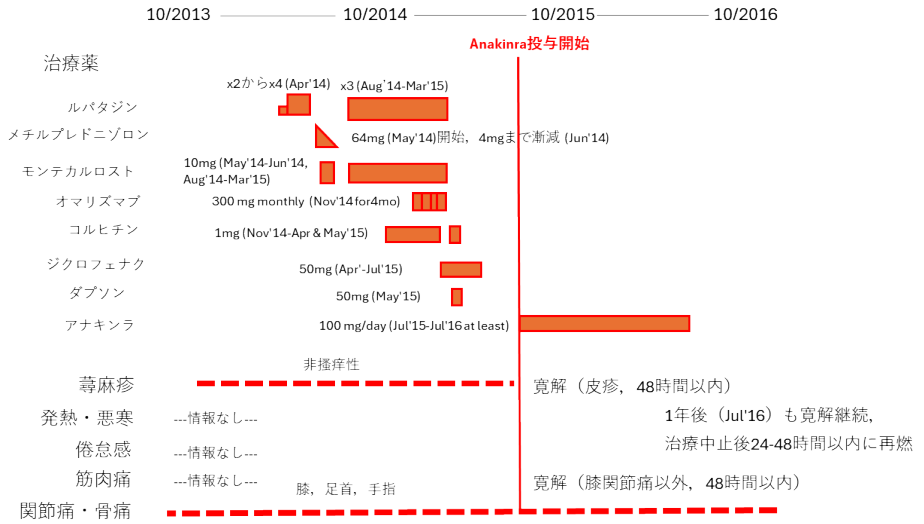
公表文献	Fank H, Caers J, Lambert M, et al. (2018) Schnitzler syndrome associated with hairy cell leukemia presenting with chronic urticaria and arthralgias. JAAD Case Rep; 4(4):386-9.
年齢/性別	50/男
罹患期間	約 3 年
初期症状	In 2013, a 50-year-old man presented with complaints of arthralgia involving knees, ankles, and fingers, which primarily manifested during the night. A few months later, he developed recurrent episodes of a nonpruritic urticarial eruption.
臨床経過	• Physical examination confirmed diffuse labile erythematous macules and wheals. The lesions usually disappeared within 24 to 48 hours without associated angioedema. • Laboratory tests found a normal blood count, increased CRP levels at 18.2 mg/L (normal, < 6.0 mg/L), and an ESR at 32 mm/h (normal, < 14 mm/h). Results were negative for antinuclear antibodies. Serum IgG, IgA, and IgM levels were within normal ranges. • In 2014, a diagnosis of spontaneous chronic urticaria was proposed, and the patient was initially treated with high doses of different antihistamines, such as rupatadine, cetirizine, and others, during 3 months without significant response. Oral corticotherapy was then administered for 1 month without any success. Next, treatment with subcutaneous omalizumab (2 × 150 mg/mo) for 6 months was proven inefficient. • In March 2015, there was an increased CRP level at 21.0 mg/L, and serum IgM was measured at 1.92 g/L (normal range, 0.4-2.3 g/L). • In April 2015, the patient was first treated with colchicine and NSAIDs, which slightly improved his symptoms. Dapsone was later added, although not tolerated by the patient. • In July 2015, anakinra, an IL-1 monoclonal antibody, was injected subcutaneously at a daily dose of 100 mg. The symptoms significantly improved within 48 hours, with the skin rash and hand and ankle arthralgia completely disappearing, yet continued mild knee arthralgia. The inflammatory parameters were negative (CRP < 1.0 mg/L), and total serum IgM decreased slightly (1.62 g/L), whereas a thin band of monoclonal IgM-k persisted. The neutrophil count decreased after anakinra initiation (1740 cells/mm^3). • In July 2016, 1 year after the first anakinra injection, the patient reported marked improvement in his quality of life, yet the skin rash systematically reappeared within 24 to 48 hours whenever therapy was discontinued. 
未治療又は既存治療での臨床症状まとめ	患者は 50 歳男性で 2013 年より関節痛及び非そう痒性蕁麻疹様発疹を発現した。2014 年より高用量の各種抗ヒスタミン薬（ルパタジン，セチリジン等），経口コルチコステロイド療法，オマリズマブを投与したが無効であった。2015 年よりコルヒチン及び非ステロイド性抗炎症薬で症状はわずかに改善，ダプソンを追加したが，忍容性を示さなかった。

Table 5-15 Hidalgo-Garcia et al. 2017

公表文献	Hidalgo-García Y, García-Fernández E, Palacio-Aller L, et al. (2017) Schnitzler Syndrome With Response to Anakinra Monotherapy: 7 Years of Follow-up. Síndrome de Schnitzler con respuesta a anakinra en monoterapia: 7 años de seguimiento. Actas Dermosifiliogr; 108(10):956-8.
年齢/性別	63/女
罹患期間	Not reported
初期症状	A 63-year-old woman with no family history of interest and who reported undiagnosed bone and joint pain since 2001.
臨床経過	• She was seen in 2007 for an 18-month history of fleeting, slightly pruritic skin lesions on her trunk and limbs, with no fever or other associated systemic symptoms. CRP was 87.5. With a diagnosis of chronic idiopathic urticaria, treatment was started with oral antihistamines with a poor response. • In January 2009, the patient developed recurrent spikes of fever that lasted 2 to 3 days and were associated with intense generalized bone pain and the appearance on her trunk and limbs of well-defined, edematous pink lesions that resolved in less than 24 hours leaving no residual lesion. Sequential treatment was started with colchicine, 100 mg/day, oral prednisone, 0.5 mg/kg/day, dapsone, 50 mg/day, and methotrexate, 15 mg/week, with no improvement. • In 2010, the patient commenced treatment with subcutaneous anakinra, 100 mg/day, leading to complete resolution of all her symptoms, including the nonspecific bone pain, within a week of starting treatment. The acute phase reactants normalized and no complications have arisen. Attempts to withdraw anakinra have led to immediate recurrence of the patient's symptoms, and she is currently asymptomatic on subcutaneous anakinra at a dose of 100 mg every 48 hours.
未治療又は既存治療での臨床症状まとめ	患者は 63 歳女性で 2001 年より骨痛及び関節痛を報告し，2007 年より体幹及び四肢に一過性の皮膚病変が 18 ヵ月間認められたため，抗ヒスタミン剤内服を開始したが効果不十分であった。2009 年より 2～3 日間持続する再発性の発熱を発現し，重度の全身性骨痛及び体幹並びに四肢の病変を伴ったため，コルヒチン，経口プレドニゾン，ダプソン，メトトレキサートによる逐次治療を開始したが，改善はみられなかった。

