

A SYSTEMATIC REVIEW OF THE CLINICAL BURDEN OF IDIOPATHIC MULTICENTRIC CASTLEMAN'S DISEASE

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INTRODUCTION

- Castleman's disease is a rare, chronically disabling and life-threatening lymphoproliferative disorder with 2 typical clinical presentations:
 - Unicentric Castleman's disease (UCD) – a slow-growing mass localised to a single lymph node site;
 - Multicentric Castleman's disease (MCD) – widespread masses that affect multiple lymph node sites and may involve other lymphatic tissues or organs, such as the spleen or liver.
- MCD can be further classified as human herpes virus 8 (HHV-8) associated, often diagnosed in HIV-infected or otherwise immunocompromised patients, or idiopathic (iMCD) .
- iMCD is associated with considerable patient suffering and potentially life-threatening complications.
- Current treatments are limited, with the international Castleman Disease Collaborative Network (CDCN) guidelines recommending siltuximab, tocilizumab or rituximab.
- A systematic review was conducted to identify the clinical burden of disease in adults with iMCD.

METHODOLOGY

- Medline and Embase were searched in December 2018 via the Ovid interface
- Two reviewers screened articles against pre-defined criteria (Table 1), whilst a third reviewer resolved discrepancies.
- One analyst extracted data using templates created in Excel, whilst another reviewer quality-controlled it.
- The DistillerSR Systematic Review Software was used in the studies selection process.

Table 1. Study inclusion criteria

PICOS	Inclusion
Population	Adult patients with MCD who are not infected with HIV and HHV-8
Intervention	- Siltuximab - Tocilizumab - Rituximab - Alone or in combination with steroids or BSC
Comparator	No restrictions
Outcomes	- Complete response - Partial response - Overall survival - AEs leading to discontinuation - Total grade 3 or higher AEs
Study design	- Clinical trials - Observational studies - Meta-analyses
Geographical scope	Worldwide
Timeframe	No restrictions
Language	No restrictions

RESULTS

- Figures 1 and 2 summarises the process for identifying the eight publications included in the review.
- Three randomised controlled trials (RCTs) and three observational studies met the inclusion criteria.

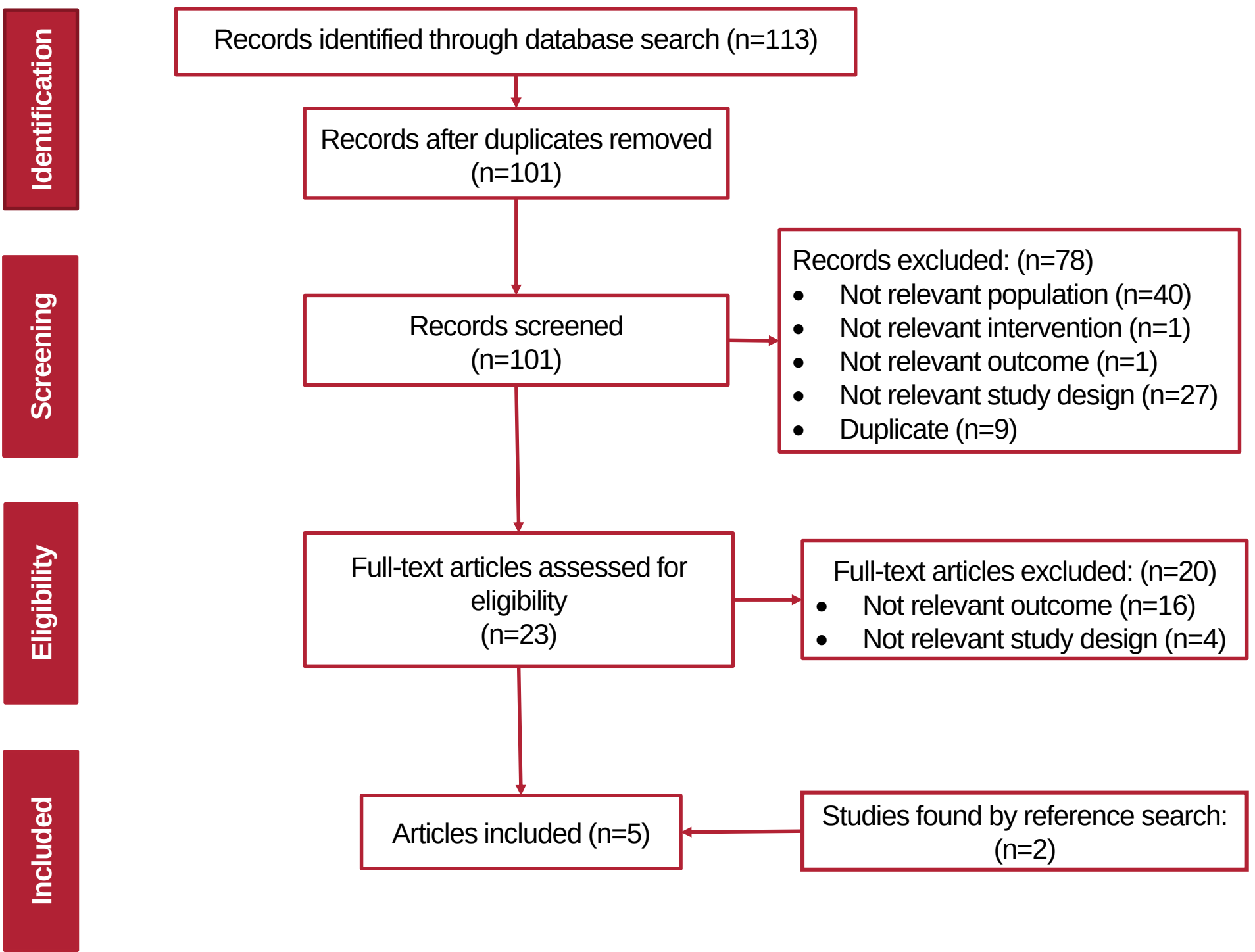


Figure 1. PRISMA diagram: Randomised control trials

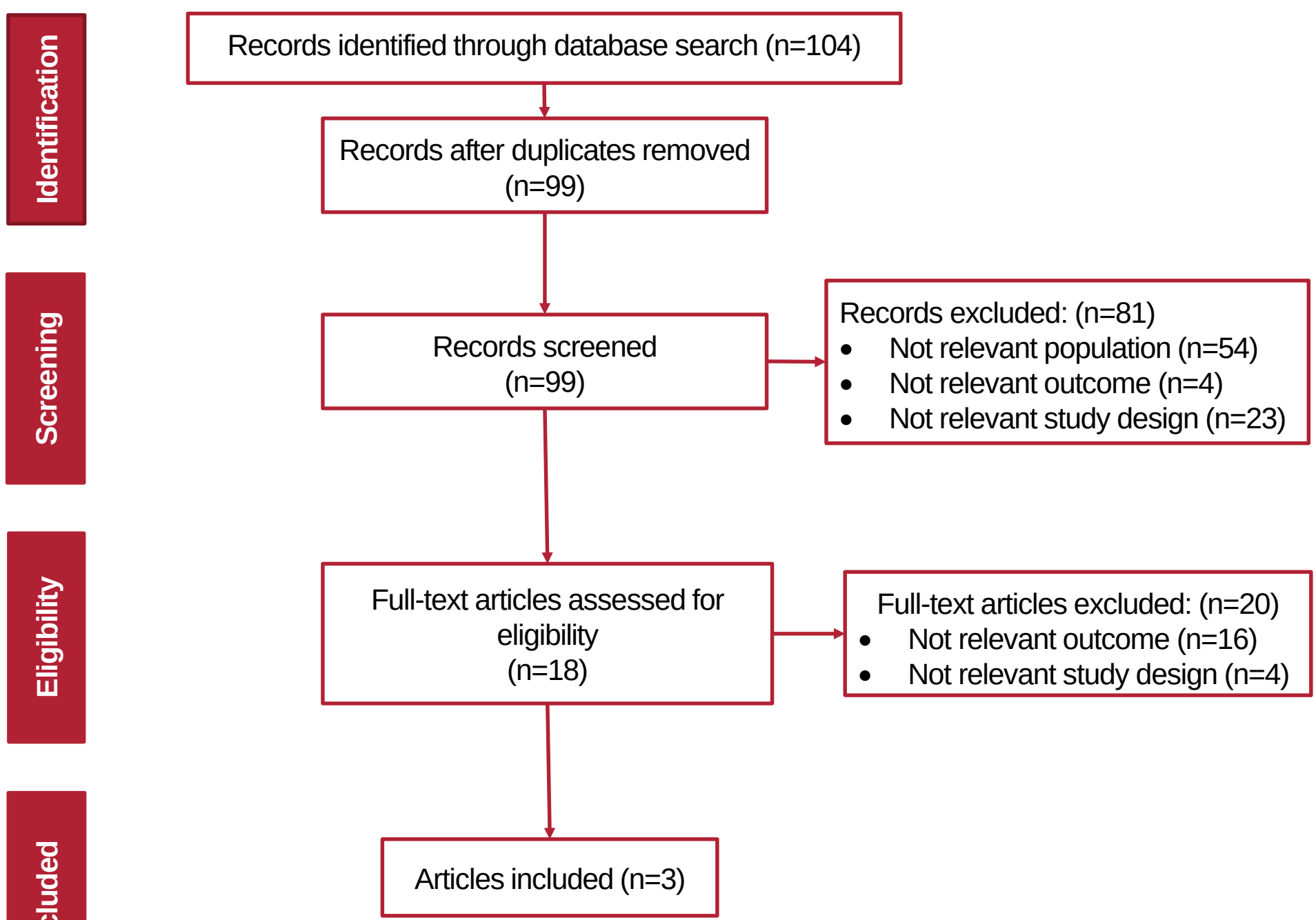


Figure 2. PRISMA diagram: Observational studies

RESULTS

Overall survival

Randomised controlled studies

- Overall survival (OS) with siltuximab ranged between 100% (year one) and 86-100% (year six) compared with 92% (year one) and 79.5% (year six) in the placebo arm.

Table 2. Overall survival reported in randomised controlled trials

Author, Year, Study number	Treatment	Outcome definition	Analysis set	Time to endpoint	N	N with event (%)
Van Rhee (2015) ¹ , NCT01400503 ²	Siltuximab	N/R	N/R	3.3 years*	19	19 (100%)
	Siltuximab	All-cause mortality (re-calculated)	SAF†	up to 6 years	60	60 (100%)
Van Rhee (2014) ³ , NCT01024036 ⁴	Siltuximab	N/R	ITT	1 year	53	53 (100%)
	Placebo	N/R	ITT	1 year	26	24 (92%)
	Siltuximab	Percent chance of survival of participants who were still alive at 6 years from the time of first study treatment	SAF‡	6 years	53	N/R (86.3%)
	Placebo		SAF‡	6 years	26	N/R (79.5%)

ITT – Intention to treat; N – Number of patients; N/R – Not reported; SAF – Safety analysis set; * - median time from the extension study onset (5.1 years from phase 1 study onset); † - All enrolled participants in this study; ‡ - All randomized participants who received at least 1 dose of study agent

Observational studies

- In the three real word evidence studies, OS varied from 75-100% among tocilizumab-treated patients.

Table 3. Overall survival reported in observational studies

Author, Year	Population	Treatment	Outcome	Outcome definition	Time to endpoint	N	N with event (%)
Kawabata (2013) ⁸	MCD patients	Tocilizumab	Overall survival	Number of deaths reported; re-calculated	N/R	12	9 (75%)
Zhai (2013) ⁹	HHV-8 and HIV-negative MCD patients	Tocilizumab	Overall survival	Number of deaths reported; re-calculated	19 months*	6	6 (100%)

HHV-8 – Human herpesvirus 8; HIV – Human immunodeficiency virus; MCD – Multicentric Castleman's disease; N – Number of patients; N/R – Not reported; * - median duration of therapy

Tumour response

Randomised controlled studies

- Complete tumour response with siltuximab was between 4-6%, and 25% of siltuximab patients achieved complete symptom response.
- No placebo-treated patient achieved a complete response.
- 34% of siltuximab-treated patients and 0% of placebo-treated patients achieved partial durable tumour and symptomatic response.
- Partial tumour response was reported in 34-48% of siltuximab-treated patients and 0-4% in the placebo arm.
- For responding subjects, median time to durable tumour and symptomatic response was 155 days vs 65 days (siltuximab vs. placebo, respectively).
- 38% of patients using placebo discontinued due to adverse events vs. 0-33% of patients on siltuximab.

Table 4. Response rates reported in randomised controlled

Author, Year, Study number	Treatment	Outcome definition	Analysis set	N	N with event (%)	Outcome definition	N with event (%)	TOTAL CR+PR
Van Rhee (2014) ⁴ , NCT01024036	Siltuximab	Complete durable tumour and symptomatic response ^a	ITT	53	1 (2%)	Partial durable tumour and symptomatic response ^b	17 (32%)	18 (34%)
	Placebo	symptomatic response ^a	ITT	26	0 (0%)	symptomatic response ^b	0 (0%)	0 (0%)
	Siltuximab	Complete tumour response assessed by investigators ^c	ITT	53	3 (6%)	Partial tumour response assessed by investigators ^d	24 (45%)	27 (51%)
	Placebo	tumour response assessed by investigators ^c	ITT	26	0 (0%)	tumour response assessed by investigators ^d	0 (0%)	0 (0%)
	Siltuximab	Complete tumour response assessed by independent radiological review ^e	ITT	53	2 (4%)	Partial tumour response assessed by the independent radiological review ^d	18 (34%)	20 (38%)
	Placebo	tumour response assessed by independent radiological review ^e	ITT	26	0 (0%)	Partial tumour response assessed by the independent radiological review ^d	1 (4%)	1 (4%)
Van Rhee (2010) ¹⁰ , NCT00412321	Siltuximab †	Complete radiologic tumour response ^c	Interim analysis	23	1 (4%)	Partial radiologic tumour response ^d	11 (48%)	12 (52%)
Van Rhee (2008) ¹¹ , NCT00412321	Siltuximab ‡	Complete tumour response ^e confirmed by the independent radiological review	Interim analysis	11	1 (9%)	Partial tumour response confirmed by the independent radiological review	5 (46%)	6 (55%)

ITT – Intention to treat; N – Number of patients; † - all doses (6, 9, 12 mg/kg) combined; ‡ - 12 mg/kg; ^adefined as a complete response by modified Cheson criteria (adjusted to assess cutaneous lesions) with improvement or stabilisation of disease-related symptoms for at least 18 weeks; ^bdefined as a partial response by modified Cheson criteria (adjusted to assess cutaneous lesions) with improvement or stabilisation of disease-related symptoms for at least 18 weeks; ^cdefined as a complete response by modified Cheson criteria (adjusted to assess cutaneous lesions); ^ddefined as a partial response by modified Cheson criteria (adjusted to assess cutaneous lesions); ^edefined by modified International Working Group criteria

Observational studies

- 33.3% siltuximab-treated patients with relapsed/refractory iMCD achieved complete response, whereas 25% of tocilizumab-treated patients had complete resolution of symptoms.

RESULTS

Table 5. Response rates reported observational studies

Author, Year	Population	Treatment	Outcome	N	N with event
Kawabata (2013) ⁸	MCD patients	Tocilizumab	Complete symptom resolution**	12	3 (25%)
Tonialini (2018) ¹²	HHV-8 and HIV-negative patients with relapsed/refractory MCD	Siltuximab	Complete response*	9	3 (33%)
	HHV-8 and HIV-negative patients with relapsed/refractory MCD: plasmacytic subtype			2	1 (50%)
	HHV-8 and HIV-negative patients with relapsed/refractory MCD: mixed subtype			5	2 (40%)
	HHV-8 and HIV-negative patients with relapsed/refractory MCD: hyaline vascular subtype			2	0 (0%)

* Complete resolution of all MCD-related symptoms including lymphadenopathy and anemia
** A complete response with simultaneous disappearance of symptoms, assessed radiologically and by clinical benefit response. Responses were defined by modified 2007 IWG Criteria (adjusted to assess cutaneous lesions)

Adverse events

Randomised controlled studies

- Adverse events (AEs) leading to discontinuation occurred in 0-23% with siltuximab in the various studies, compared to 38% of patients treated placebo, respectively.
- Grade ≥3 AEs occurred in 42-48% and 54% of patients in siltuximab and placebo treatment arms, respectively.
- Observational studies
 - In a small registry with 9 patients, no patients experienced Grade ≥3 AEs with siltuximab.
 - Four out of 21 patients had used tocilizumab for over 6 years without any side effects in a Japanese patient cohort.

DISCUSSION

- Unsurprising for a rare disease, the evidence for the clinical burden of iMCD was scarce.
- Additionally, the sample size in the published studies were generally small and the definitions of response differed between studies.
- Siltuximab was the only treatment with outcomes supported by randomised controlled studies
- The only evidence for tocilizumab was from observational studies with small patient numbers.
- No evidence was found that supported the use of rituximab in iMCD patients.

CONCLUSIONS

- Studies relating to the treatment adults with MCD who are not infected with HIV and HHV-8 are limited.
- Of the three CDCN recommended treatments, siltuximab's use is supported by the strongest evidence in iMCD.

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DISCLOSURE

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B Smela-Lipińska, C Marre, I Myjak, P Szawara, E Abdennadher and M Toumi are employees of Creativ-Ceutical, P Okhuoya is an employee of EUSA Pharma and SE Marsh is an employee of PharmEkon Ltd, providing paid services to EUSA Pharma.