HEALTH-RELATED QUALITY OF LIFE AND PATIENT REPORTED OUTCOMES MEASURES IN IDIOPATHIC MULTICENTRIC CASTLEMAN'S DISEASE: A SYSTEMATIC REVIEW

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INTRODUCTION

- Castleman's disease is a rare 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 sustained morbidity and recurrent exacerbations.
- This systematic review aimed to identify and quantify the humanistic 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 (Evidence Partners, Ottawa, Canada) 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/or HHV-8
Intervention	No restrictions
Comparator	No restrictions
Outcomes	• Health related quality of life (HRQoL) • Patient reported outcomes (PROs) • Patient satisfaction
Study design	• Cohort studies • Cross-sectional studies • Registries • Claims analyses • Meta-analyses • Clinical trials (humanistic burden review)
Geographical scope	Worldwide
Timeframe	From 2008
Language	No restrictions

RESULTS

- Figure 1 summarises the process for identifying the five[1-5] publications included in the review.
- All five studies were in patients treated with siltuximab.

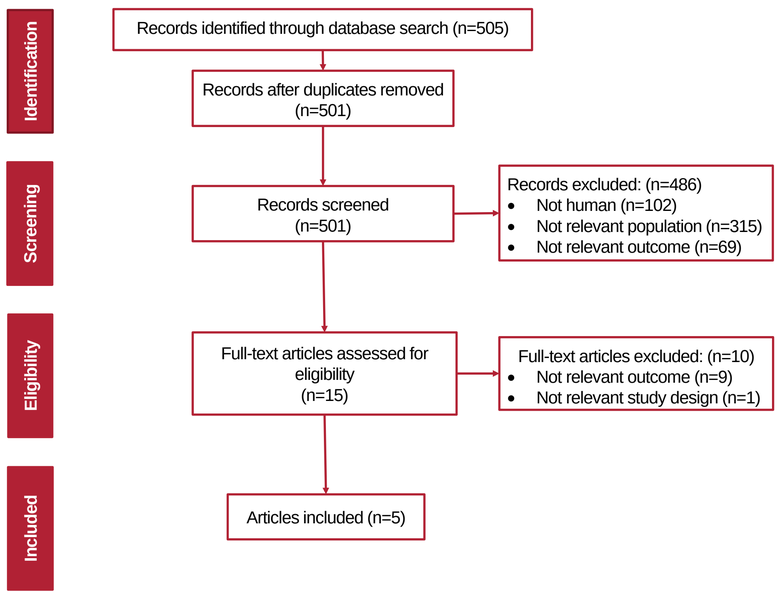

Figure 1. PRISMA diagram

- Patient reported outcomes (PROs) and health-related quality of life (HRQoL) were measured using the
  - Multicentric Castleman Disease Symptom Scale (MCD-SS) (1 study, 4 publications),
  - FACIT-Fatigue questionnaire (1 study, 2 publications), and
  - SF-36 (1 study, 3 publications)

MCD-SS results

- At baseline, the mean and median number of symptoms reported by severity was 9.2 and 9.5 (out of 16), respectively.[1,2]
- Symptoms reported most frequently were very mild and mild: shortness of breath (40%), lack of energy (33%), feeling weak (33%), tiredness (32%) and pain (32%).[1] (Figure 2)
  - Items in the *Fatigue* domain (tiredness, lack of energy, feeling weak and fatigue) had the highest severity.[1]
  - Siltuximab-treated subjects reported significant and durable improvements in fatigue compared with subjects in the placebo arm in the *Fatigue* domain.
  - These improvements were observed at the end of Cycle 1 and throughout the study.

RESULTS

MCD-SS results (continued)

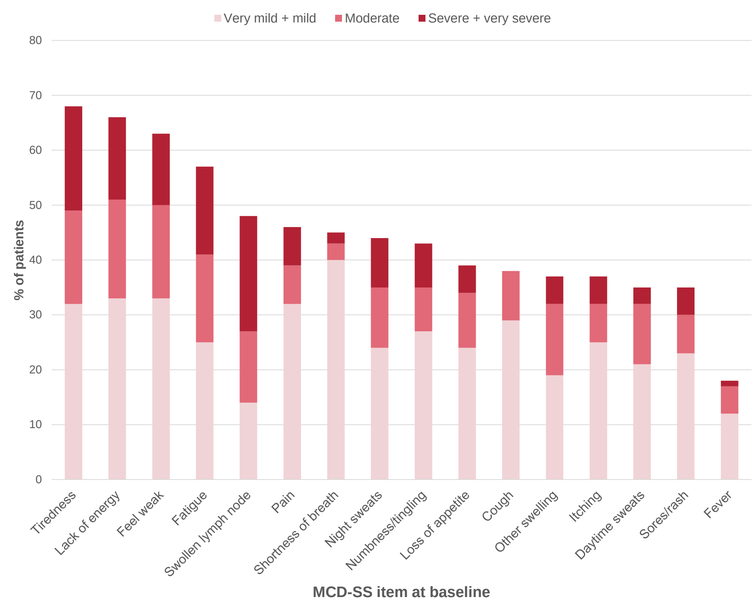

Figure 2. Frequency & severity of symptoms reported according to MCD-SS individual items

FACIT-F results

- At baseline, >50% patients reported lower fatigue scores than the normal population in the United States (population mean score = 44 out of 52; higher scores indicates less severity)
- Both siltuximab and placebo treated patients had comparable mean total score at baseline (32.4 vs 31.0) (Figure 3)
  - Siltuximab-treated patients reported much higher mean values than the patients on placebo during follow-up (38.6 vs 26.9, respectively). (Figure 3)
  - More siltuximab-treated patients achieved a score of ≥44, with durability of 120 days or more, than on the placebo group (35% vs. 11%; p=0.0475)

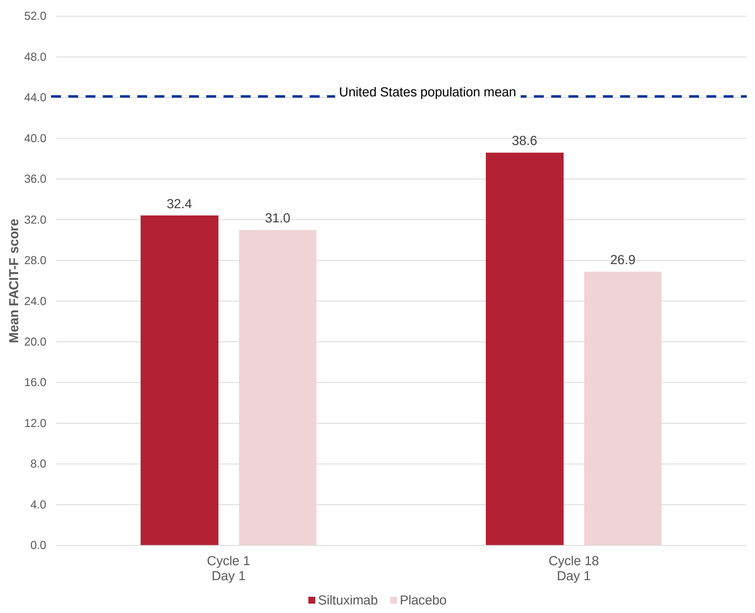

Figure 3. Change in FACIT-F scores over study duration period

SF-36 results

- Treatment with siltuximab more often resulted in an SF-36 score equal to, or greater than the population norm in the respective study at final visit compared with placebo. (Figure 4)

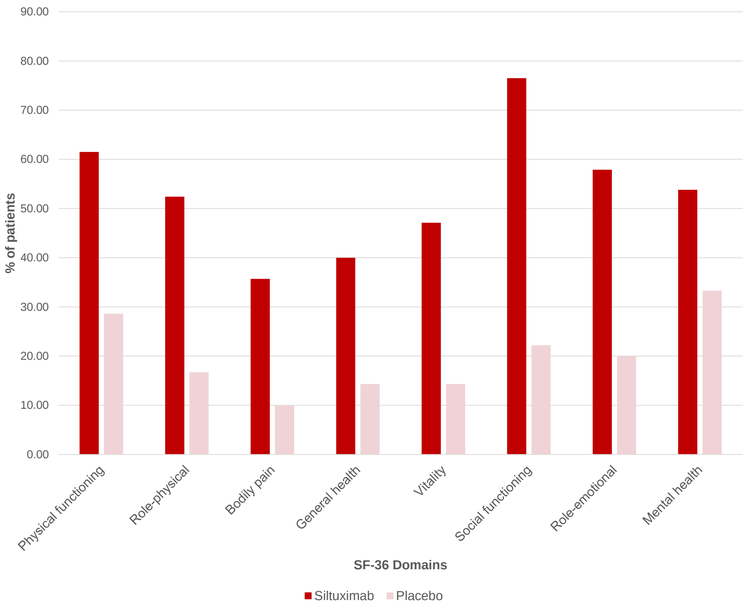

Figure 4. Proportion of patients achieving an SF-36 domain score equal to, or greater than, the population norm at final visit

- Significant improvements were reported for subjects in the siltuximab treatment arm across 5 of the 8 SF-36 domains compared with placebo
- In a post hoc analysis[5] using the SF-36 items related to depressed mood and anhedonia, siltuximab showed a significant reduction in depressive symptoms in patients with prevalent depressed mood or anhedonia compared with placebo.

RESULTS

SF-36 results (continued)

- In a separate analysis[6], the SF-36 results were transformed into SF-6D scores and mapped to the EQ-5D. (Figure 5)
  - At baseline, mean utility values for both treatment groups were comparable
  - Siltuximab treated patients reported a trend towards improvement of utility values within follow-up, but the same trend was not observed in the placebo-treated patients

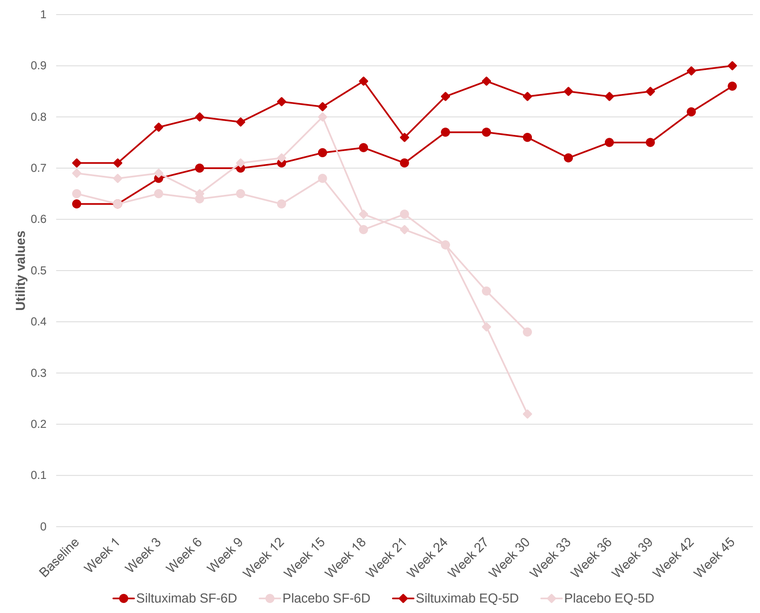

Figure 5. SF-6D and EQ-5D Utilities derived from SF-36

DISCUSSION

- Siltuximab-treated patients consistently reported significant improvements in fatigue compared with placebo across 2 PRO instruments (FACIT-F and MCD-SS Fatigue).
- These significant improvements were observed early (within ~2 months) and maintained over the study period.
- A numerically greater proportion of siltuximab-treated patients 'returned to normal' (i.e. asymptomatic fatigue status) compared with placebo-treated patients.
- Additionally, significant improvements in physical and mental aspects of health were reported with siltuximab compared with placebo for the SF-36 instrument, indicating that compared with placebo:
  - siltuximab significantly improved vitality,
  - siltuximab significantly reduced bodily pain,
  - siltuximab significantly improved ability to perform daily activities,
  - siltuximab significantly improved overall mental health/emotional well-being,

CONCLUSIONS

- Due to the rarity of the disease data is limited, but iMCD is associated with poor outcomes, as reported by patients.
- Available data showed that siltuximab was associated with rapid and sustained improvements in fatigue, functioning and well-being compared with placebo.

REFERENCES

1. van Rhee F, et al. Patient-reported Outcomes for Multicentric Castleman's Disease in a Randomized, Placebo-controlled Study of Siltuximab. Patient. 2015; 8(2): 2017-16
2. Casper C. et al. The Multicentric Castleman's disease (MCD)-symptom scale (MCD-SS): Development and validation of a patient-reported outcome (PRO) measure for an ultra-orphan disease. Value in Health. 2014:17(7): A535
3. Van Rhee F et al. Superior restoration of health with siltuximab among Multicentric Castleman's Disease patients when measured by SF-36. Blood. 2014:124(21): 4469
4. Van Rhee F et al. Improvements in hemoglobin levels and fatigue in a randomized, double blinded, placebo controlled study (MCD3282001) of siltuximab in patients with Multicentric Castleman's disease (MCD). Haematologica. 2014: 99(SUPPL. 1): 464-65
5. Sun Y, et al. The effects of interleukin-6 neutralizing antibodies on symptoms of depressed mood and anhedonia in patients with rheumatoid arthritis and multicentric Castleman's disease. Brain, Behavior, and Immunity. 2017: 66; 156-64
6. Vernon M et al. Deriving health utility values from a randomized, double-blind, placebo-controlled trial of siltuximab in subjects with Multicentric Castleman's Disease. Current Medical Research and Opinion. 2016:32(7):1193-200

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DISCLOSURE

EUSA Pharma financially sponsored this project and participated in the interpretation of results, writing, review and approval of the abstract and poster. The project was executed by Creativ-Ceutical under a service agreement with EUSA Pharma.

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.

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