BLOOD-BASED MASS SPECTROMETRY MRD TRACKING (M-INSIGHT) IN MULTIPLE MYELOMA PATIENTS FROM CLINICAL TRIAL NCT02513186

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INTRODUCTION

Multiple Myeloma (MM) is a type of cancer of the bone marrow characterized by an anormal growth of the number of plasma cells, which produce a monoclonal antibody (M-protein). Measurable residual disease (MRD) is an important prognostic factor in multiple myeloma to evaluate the depth of treatment response widely used in clinical trials[1].

M-protein is a well-established biomarker used for MM diagnostic and monitoring. Mass spectrometry (MS) has been introduced as a possible tool to monitor M-protein[2]. Intact protein measurement by MS has the drawback of lacking sensitivity with high interference from the polyclonal background, in contrast**,** clonotypic peptides originating from the variable region of the M-protein are unique for each patient relieving this interference[3].

M-InSight (Sebia), an innovative ultra-sensitive technique that allows quantitation of the M-protein in blood, uses cutting-edge mass spectrometry (MS) techniques which detect and quantify clonotypic peptides[4], allowing to track low M-protein levels and to detect loss of disease control earlier than conventional biochemical assays (such as SPEP).

RESULTS

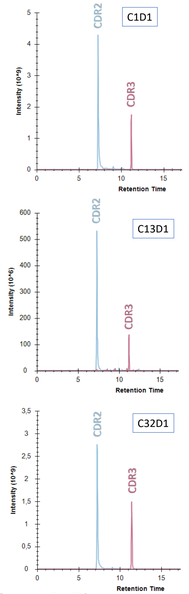

Figure 2, *Chromatogram of 2 targeted peptides at 3 different time points (Patient A)*

Patient	A	B	C
Isotype	FLC kappa	IgG, Kappa	IgG, Lambda
M-spike (g/dL)	0	1.9	3.3
Treatment	Isatuximab	Isatuximab	Isatuximab
Fold change	1/100	1/50	1/30000

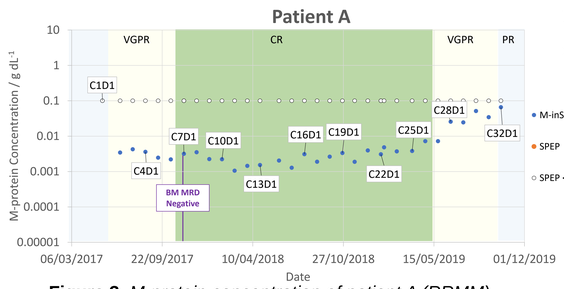

Figure 3, *M-protein concentration of patient A (RRMM) that reached CR, followed by a relapse*

2 peptides have been selected from the patient A kappa light chain. One peptide located in the CDR2 and one located in the CDR3 region. Their peak areas are represented in figure 2 at 3 different time points; Before treatment (C1D1), lowest concentration monitored (C13D1) and last time point (C32D1). MRD results correspond to 10^{-6} sensitivity by NGS assay.

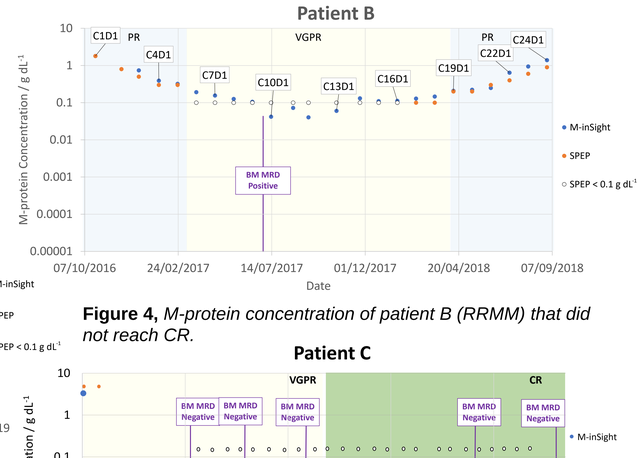

Figure 4, *M-protein concentration of patient B (RRMM) that did not reach CR.*

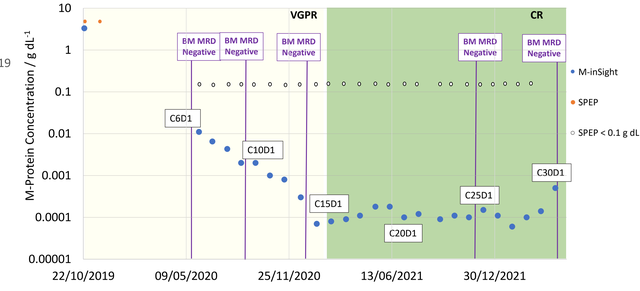

Figure 5, *M-protein concentration of patient C (NDMM) with a sustained MRD.*

In this study, M-insight was able to monitor the disease on 5 patients that had sustained MRD (consecutive MRD negativity) showing controlled disease (no increase or decrease of M-protein measured by M-insight by 2-fold for 2 consecutive time points) such as patient C.

Similar to patients A and B, 4 patients had an increase of M-protein measured by M-insight of at least 2-fold in 2 consecutive time points showing that M-InSight was able to provide an earlier detection of potential loss of disease control compared to SPEP which was still negative for 3 of these patients.
Only one patient had M-insight unmeasurable M-protein concentration, staying unmeasurable for 1 year and negative by NGS MRD.

M-insight was shown to be highly concordant with Bone Marrow (BM) MRD (Table 1). 100% of patients that were MRD positive by NGS 10^{-6} were MS-MRD positive and could be quantified by M-InSight.
The lowest M-protein concentration measured by M-InSight was 0.01 mg/dL (10 µg/dL).

Concordance of 26 paired samples (same timepoint)		M-inSight +	M-inSight -
BM MRD	+	16	0
	-	6	4

Table 1, *Concordance between M-InSight and BM MRD among patients included in this study.*

MATERIALS AND METHODS

Samples from 15/18 newly diagnosed (NDMM) non eligible for transplantation MM patients from a Sanofi clinical trial (NCT02513186) were chosen to monitor MRD by M-InSight. All patients were selected from the VRDI Part B (bortezomib, lenalidomide, dexamethasone).

Samples from 3/18 patients with relapsed and refractory MM (RRMM) were selected from NCT02812706 study. The treatment included administration of isatuximab once every week for 4 weeks followed by once every other week.

M-protein in serum was de-novo sequenced using mass spectrometry based analysis to identify unique clonotypic peptides for each patient. Each unique peptide was quantified using high resolution nLC-MS/MS (Liquid Chromatography tandem MS).

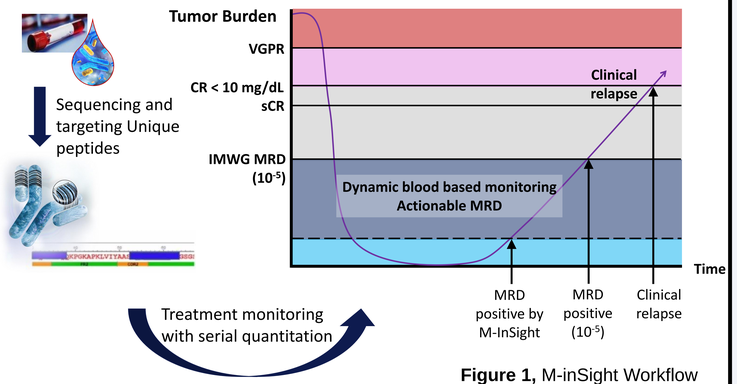

Figure 1, M-inSight Workflow

CONCLUSIONS

- M-protein quantification was highly concordant with the one obtained by SPEP when available (Pearson R=0.78, p<0.01)
- 100% of patients that were MRD positive by NGS 10^{-6} were MS-MRD positive and could be quantified by M-InSight
- 60% of patients that were MRD negative by NGS 10^{-6} were still positive and quantifiable by M-InSight, suggesting higher sensitivity
- M-insight was able to monitor the disease on 5 patients that had sustained MRD (consecutive MRD negativity) showing controlled disease (no increase or decrease of M-protein by 2-fold for 2 consecutive time points)
- Results show that M-Insight is capable to monitor M-protein concentration where other methods can't and provides information about a loss of disease control earlier than conventional biochemical assays (such as SPEP).

REFERENCES

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