Impact of the IF system using HYDRASHIFT® on response evaluation for patients under treatment with the IgG-κ monoclonal antibody isatuximab

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Introduction

- Serum immunofixation (IF) is required to confirm a complete response (CR) in the treatment of multiple myeloma (MM) (1).
- Isatuximab is an anti-CD38 IgG-κ monoclonal antibody (mAb) which is detected by IF and interferes with the interpretation of CR.
- The HYDRASHIFT 2/4 Isatuximab (HYDRASHIFT Isa IF assay) was developed by Sebia with Sanofi to remove this interference and thereby assist in accurate clinical assessment (2). It was used to determine the final CR rate in the IKEMA study (3,4).
- We used different IF systems to analyze the sera of MM patients on treatments including isatuximab to examine the differences in M-protein detection ability and CR assessment.

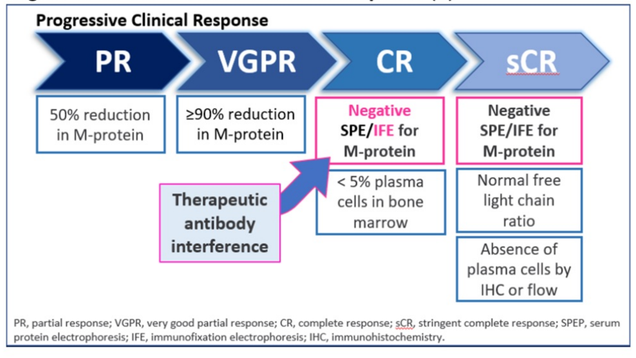
Patients and Methods

Serum samples from five patients under isatuximab treatment were tested and monitored with IF on the HYDRASYS2 system (Sebia) using HYDRASHIFT 2/4 isatuximab kit (Sebia) and with IF on the Epalyzer2 system (Helena). Serum free light chain (FLC) and immunoglobulin (IG) concentrations were also measured.

HYDRASHIFT/HYDRASYS: The IF assay on the HYDRASYS2 system (Sebia) using HYDRASHIFT 2/4 isatuximab kit (Sebia)
Epalyzer: The IF assay on the Epalyzer2 system (Helena)

Documented Detection Sensitivity of M-Protein on two IF systems
HYDRASYS：25mg/dL on IgG, IgA, IgM, Light Chain κ, λ
Epalyzer： IgG 50mg/dL, IgA 50mg/dL, IgM 110mg/dL, No description for Light Chains

Figure 1. IMWG Criteria for Clinical Response (1)



PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response; SPEP, serum protein electrophoresis; IFE, immunofixation electrophoresis; IHC, immunohistochemistry.

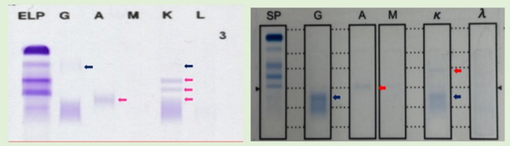
Results

Table 1. Patient characteristic at the time of response assessment

No	Age /Sex	MM subtype	Creatinine clearance+ (mL/min)	Detected Type of M-protein		serum IGs (mg/dL)			serum FLCs (mg/L)			Response Evaluation By HYDRASHIFT
				HYDRASHIFT /HYDRASYS	Epalyzer	IgG	IgA	IgM	κ	λ	κ/λ	
1	71/F	IgG-λ	56.2	Not Detected	IgG-κ	276	11	3	< 0.5	1.7	< 0.29	CR
2	58/M	IgG-κ	46.6	IgG-κ	IgG-κ	2473	4	3	4.1	0.5	8.20	PD
3	73/M	BJP-κ	21.2	IgA-κ, free-κ x 2	IgG-κ, IgA-mono*, Free-κ	269	48	9	1585	6.9	229.7	PD
4	79/F	IgA-κ, BJP-κ	27.8	Not Detected	IgG-κ	122	8	2	< 0.5	0.8	< 0.63	CR
5	49/M	IgG-λ	84.5	IgG-λ	IgG-κ, IgG-λ	362	17	7	< 0.5	1.3	< 0.38	VGPR

+Creatinine clearance was calculated by Cockcroft-Gault formula. *IgA-mono: Epalyzer did not detect the kappa of IgA-κ so they were judged as IgA-mono.

Figure 2 Comparison between two IF systems in Patient 3
A: The IgG-κ originating from isatuximab was shifted (blue arrows) and the type of M-protein was judged as IgA-κ and two free kappa (red arrows), indicating single and polymerized free kappa, which is consistent with severe renal impairment and a high level of serum FLC-κ.
B: Isatuximab was judged as the IgG-κ type M-protein (blue arrows). IgA band was detected without corresponding kappa, and only one free kappa band was detected (red arrows).



A. IFE using **HYDRASHIFT/HYDRASYS** B. IFE using **Epalyzer**

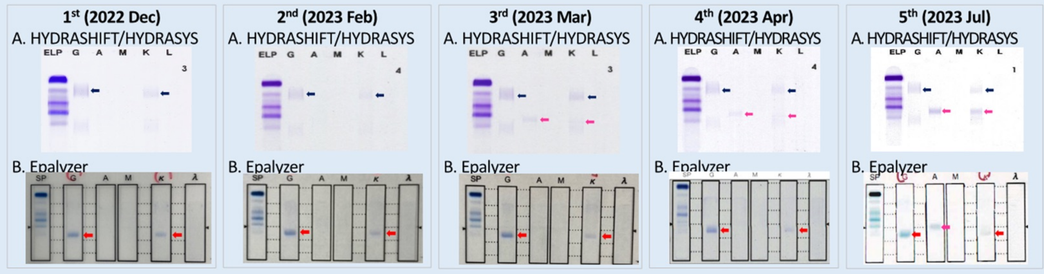


Figure 3. Changes in M proteins by each detection method during the course of treatment in patient 4
A: **HYDRASHIFT/HYDRASYS**: the IgG-κ originating from Isatuximab was shifted to the α-region (blue arrows), so M-protein was not detected in the γ-region until the 2nd point. From the 3rd point, the IgA-κ type M-protein was detected (red arrows) and the concentration of IgA slightly increased to 11mg/dL.
B: **Epalyzer**: the IgG-κ originating from Isatuximab (red arrows) was detected as M-protein, and did not detect IgA till the 5th point, which was 4 months later when the concentration of IgA increased to 69mg/dL.

Table 2. Changes in IgGs and FLC levels in patient 4

Monitoring Point		1st (2022 Dec)	2nd (2023 Feb)	3rd (20223Mar)	4th (2023 Apr)	5th (2023 Jul)
M-protein Detection	**HYDRASHIFT/HYDRASYS**	Not Detected	Not Detected	**IgA-κ**	**IgA-κ**	**IgA-κ**
	Epalyzer	IgG-κ	IgG-κ	IgG-κ	IgG-κ	IgG-κ, **IgA-mono***
serum IgGs (mg/dL)	IgG	122	94	107	96	51
	IgA	8	7	**11**	**16**	**69**
	IgM	2	3	3	2	4
serum FLC (mg/L)	κ	< 0.5	4.3	7.0	13.9	145.6
	λ	0.8	0.8	0.9	0.8	0.6
	κ/λ	< 0.63	5.38	7.78	17.38	242.7

- The median age of the patients (3 males and 2 females) was 73 years (range; 49-79).
- In Patient 3, who had severe renal impairment and high serum FLC, an IgA-κ band and two free kappa monoclonal bands (BJP-κ) were detected by HYDRASHIFT/HYDRASYS (Fig. 1-A) while Epalyzer only detected an IgA band with no associated light chain and one weak BJP-κ band, as well as IgG-κ from isatuximab (Fig. 1-B).
- During monitoring, Patient 4 detected a weak IgA-κ indicating disease progression (Fig. 2-A). However, Epalyzer did not detect this IgA-κ and only detected IgG-κ originating from isatuximab (Fig. 2-B).
- The HYDRASHIFT/HYDRASYS completely removed the isatuximab-derived IgG-κ band from the gamma region and correctly assessed CR in 2 patients.

Discussion

- The HYDRASHIFT/HYDRASYS showed higher sensitivity and specificity for M-protein detection, correctly identifying serum free-κ (BJP-κ) and a low level of M-protein (IgA-κ) which the Epalyzer did not detect. These results suggest that the response and CR assessments of patients would differ depending on the IF system used.
- In clinical practice of MM in patients under isatuximab, the use of HYDRASHIFT/HYDRASYS showed good performance regarding M-protein interpretation and accurate CR assessment. These studies suggest that a "CR" assessment of isatuximab-treated patients would be increased by use of HYDRASHIFT/HYDRASYS.

Conclusions

- The **M protein Detectability** and **Clinical Response** of patients could differ depending on the IF system used.
- The HYDRASHIFT/HYDRASYS has high sensitivity and specificity for detecting M-proteins, especially BJP and small M-proteins.
- The HYDRASHIFT/HYDRASYS showed good performance regarding the proper CR assessment for Patients under isatuximab.

References

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Disclosures

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