FECAL LACTOFERRIN, CALPROTECTIN, PMN-ELASTASE, CRP AND WHITE BLOOD COUNT AS INDICATORS FOR MUCOSAL HEALING AND CLINICAL COURSE IN ULCERATIVE COLITIS: A PROSPECTIVE 12-MONTH MONITORING STUDY

UNIVERSITÄT DUISBURG ESSEN

Open-Minded

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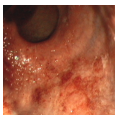
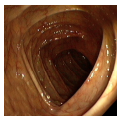
Introduction

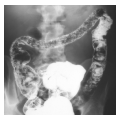
Ulcerative colitis (UC), characterized by periods of active disease and remission, is challenging to manage. Recent studies have identified mucosal healing as an optimal patient outcome.



Aims

In this study, we investigated whether blood and fecal biomarkers of inflammation are able to distinguish between mucosal healing defined by endoscopy from intestinal inflammation, to differentiate between clinical remission and sustained clinical remission and to show predictive value for a flare if levels at baseline are elevated.





Methods

Endoscopy (Index EI - Rachmilewitz <=1 indicating mucosal healing) (baseline, 12 month), clinical activity index (CAI - Rachmilewitz), fecal Lactoferrin (FLA; cut-off: >=7.25µg/g), Calprotectin (CAL;>50µg/g) and PMN-Elastase (PMN-e;>0.062µg/g), serum CRP (≥0.5mg/dl) and white blood count (WBC>8.5/nl) (baseline, 1, 3, 6, 9, 12 month) were determined repeatedly and in events of acute flares.

Table 1: Median, range and p-values of the five diagnostic biomarkers according to the three groups: Patients in an acute clinical flare (CAI > 4), patients in clinical remission (CAI≥2 and ≤4) and patients in sustained clinical remission (CAI < 2, normal bowel frequency and no blood in stool) as **defined by the CAI**.

Diagnostic tool	Acute clinical flare CAI>4	clinical remission CAI≥2 and ≤4	sustained clinical remission CAI<2	p-value from Mann Whitney U
median ± STD	N = 52	N = 119	N = 358	
Lactoferrin	33.1 (0.1 – 145.0)	20.0 (0.1 – 167.6)		0.109
	33.1 (0.1 – 145.0)		3.6 (0.0 – 160.7)	***< 0.000***
		20.0 (0.1 – 167.6)	3.6 (0.0 – 160.7)	***< 0.000***
Calprotectin	25.0 (1.7 – 105.6)	19.2 (0.01 – 365.5)		0.057
	25.0 (1.7 – 105.6)		9.2 (0.01 – 369.3)	***< 0.000***
		19.2 (0.01 – 365.5)	9.2 (0.01 – 369.3)	***0.004***
PMN-elastase	0.06 (0.0 – 0.4)	0.04 (0.0 – 0.4)		***0.034***
	0.06 (0.0 – 0.4)		0.02 (0.0 – 0.7)	***< 0.000***
		0.04 (0.0 – 0.4)	0.02 (0.0 – 0.7)	***0.022***
CRP	0.5 (0.1 – 10.6)	0.2 (0.1 – 9.9)		0.051
	0.5 (0.1 – 10.6)		0.2 (0.0 – 3.0)	***< 0.000***
		0.2 (0.1 – 9.9)	0.2 (0.0 – 3.0)	***0.004***
White blood count	7.3 (3.0 – 14.7)	6.6 (2.7 – 13.7)		***0.011***
	7.3 (3.0 – 14.7)		6.3 (3.1 – 14.9)	***< 0.000***
		6.6 (2.7 – 13.7)	6.3 (3.1 – 14.9)	0.054

Diagnostic tool		sensitivity in %	specificity in %	PPV in %	NPV in %
Lactoferrin	n = 515	63	63	54	70
Calprotectin 50	n = 515	8	98	75	60
PMN-elastase	n = 515	34	86	63	64
CRP	n = 526	32	87	66	83
white blood count	n = 529	23	90	63	61

Table 2: Sensitivity and specificity, PPV and NPV for the five diagnostic biomarkers compared to sustained clinical remission **(CAI < 2, normal bowel frequency and no blood in stool) as gold standard**

Table 4: Sensitivity and specificity, PPV and NPV for the five diagnostic biomarkers compared to mucosal healing using **endoscopy as gold standard**

Diagnostic tool		sensitivity in %	specificity in %	PPV in %	NPV in %
Lactoferrin	n = 515	63	63	54	70
Calprotectin 50	n = 515	8	98	75	60
PMN-elastase	n = 515	34	86	63	64
CRP	n = 526	32	87	66	83
white blood count	n = 529	23	90	63	61

Table 5: Sensitivity and specificity, area under the curve and p- value for ROC analyses, relative risk with elevated biomarkers at baseline to develop a flare within the study.

Diagnostic tool		Cut-off	AUC (95% CI)	sensitivity in %	specificity in %	Diagnostic accuracy in %	p-value	RR (95% CI), p-value
Lactoferrin	n = 161	11.9	0.734 (0.654 – 0.813)	70.3	70.1	70.2	***< 0.000***	***1.99 (1.47 – 2.71), p<0.001***
Calprotectin 50	n = 161	13.9	0.700 0.619 – 0.782]	64.1	63.9	64.0	***< 0.000***	***1.58 (1.20 – 2.09), p=0.001***
PMN-elastase	n = 163	0.035	0.697 (0.614 – 0.780]	54.7	73.2	64.0	***< 0.000***	***1.67 (1.21 – 2.29) p<0.001***
CRP	n = 151	0.25	0.651 (0.562 – 0.740	62.1	62.9	62.5	***0.001***	***1.52 (1.15 – 2.0) p=0.002***
White blood count	n = 166	n.s.	0.569 (0.477 – 0.660]	n.s	n.s		0.133	

Table 3: Median levels and p-values of the five diagnostic biomarkers according to the three groups: Patients in an acute clinical flare and endoscopic intestinal inflammation, patients in clinical remission and endoscopic intestinal inflammation, Patients in clinical remission and mucosal healing as **defined by the CAI and endoscopy**.

Diagnostic tool median (range)	clinically active intestinal inflammation N = 35	in clinical remission intestinal inflammation N = 37	Mucosal healing N = 107	p-value from Mann Whitney U test
Lactoferrin	43.7 (0.1 – 145.0)	36.7 (0.2 – 160.7)		0.687
	43.7 (0.1 – 145.0)		4.4 (0.0 – 126.9)	***< 0.000***
		36.7 (0.2 – 160.7)	4.4 (0.0 – 126.9)	***< 0.000***
Calprotectin	25.0 (1.7 – 105.6)	19.8 (1.4 – 98.5)		0.292
	25.0 (1.7 – 105.6)		10.4 (0.01 – 62.1)	***< 0.000***
		19.8 (1.4 – 98.5)	10.4 (0.01 – 62.1)	***0.003***
PMN-elastase	0.06 (0.0 – 0.4)	0.03 (0.0 – 0.4)		0.052
	0.06 (0.0 – 0.4)		0.02 (0.0 – 0.7)	***< 0.000***
		0.03 (0.0 – 0.4)	0.02 (0.0 – 0.7)	***< 0.011***
CRP	0.7 (0.1 – 10.6)	0.2 (0.2 – 9.9)		***0.011***
	0.7 (0.1 – 10.6)		0.2 (0.0 – 2.8)	***< 0.000***
		0.2 (0.2 – 9.9)	0.2 (0.0 – 2.8)	0.243
White blood count	7.0 (3.0 – 14.7)	6.5 (3.7 – 13.0)		0.098
	7.0 (3.0 – 14.7)		6.4 (3.8 – 13.0)	***0.036***
		6.5 (3.7 – 13.0)	6.4 (3.8 – 13.0)	0.793

Results

In 91 patients (45 female, mean age 52±13.4 years), 620 CAI and 180 endoscopies were performed. A total of 42 (46%) patients developed a clinical flare.

Median levels for acute clinical flare (CAI >4; n= 52) vs clinical remission (CAI<5; n=119) vs sustained clinical remission (CAI<3; no fecal blood; no diarrhea; n=358) for the five biomarkers are shown in table1. Sensitivity, specificity , positive predictive value (PPV) and negative predictive value (NPV) using sustained clinical remission (CAI<3; no fecal blood; no diarrhea) as gold standard are shown in table 2.

Median levels for acute intestinal inflammation confirmed by endoscopy (n=35) vs clinical remission without mucosal healing (n=37) vs mucosal healing (n=107) for the five biomarkers are shown in table 3. Sensitivity, specificity , PPV and NPV using endoscopy as gold standard are shown in table 4.

Using pre-defined cut-offs, only FLA increased levels at baseline were associated with a significant higher risk of flaring (RR 1.69, p=0.018).

Optimized cut-offs for FLA were 11.9µg/g, CAL 13.9µg/g, PME-e 0.035µg/g and CRP 0.25mg/dl.

Using these, patients with elevated FLA at baseline had a relative risk (RR) of 1.99 (95% CI 1.47-2.71, p<0.000) to develop a flare, CAL RR=1.58, (1.20–2.09, p<0.000) PMN-e RR=1.67 (1.21–2.29, p<0.000), CRP: RR=1.52 (1.15–2.0, p<0.001) (WBC: n.s.).

Conclusion

Fecal biomarkers showed moderate correlation to endoscopy in UC for detecting mucosal healing and only fecal Lactoferrin had a median level above the pre-defined cut-off for active inflammation. Using optimized cut-offs, FLA, Cal, PMN-e and CRP were predictive of a flare.

References

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