IL-17A levels in systemic lupus erythematosus associated with inflammatory markers and lower rates of malignancy and heart damage: Evidence for a dual role

Warren Raymond1, Gro Ostli-Eilertsen2, Sheynae Griffiths1, Johannes Nossent1,2,3

Abstract

Objective: The interleukin 17 (IL-17) cytokine family is involved in a number of chronic inflammatory diseases. In spite of contradictory findings and a lack of causality in clinical studies, IL-17 inhibition for systemic lupus erythematosus (SLE) has regained attention as a potential therapeutic pathway, after demonstrating disease-modifying capabilities in ankylosing spondylitis. We investigated the clinical associations of interleukin 17 A (IL-17A) in patients with SLE.

Material and Methods: A cross-sectional study was performed involving SLE patients (n=102; age: 49 years; 86% female) recruited from a regional registry. IL-17A levels were determined by immunoassay, disease activity by Systemic Lupus Erythematosus Disease Activity Index-2K (SLEDAI-2K), and cumulative damage by Systemic Lupus International Collaborative Clinics Damage Index (SDI) scores. Non-parametric techniques were used to examine the association between IL-17A and disease activity and autoantibody profiles were compared with healthy controls (n=31): principal component analysis (PCA) was used to determine the interplay of immune cells across disease states and damage development in SLE patients.

Results: SLE patients had higher IgG levels, lower T-cell and B-cell counts, but median IL-17A levels did not differ from the controls (28.4 vs. 28.4 pg/mL, p=0.9). In SLE patients, IL-17A did not correlate with SLEDAI-2K or SDI, but was inversely related with age (correlation coefficients, Rs=–0.29, p<0.05), systolic blood pressure (Rs=–0.31, p<0.05), years of smoking (Rs=–0.43, p<0.05), cumulative heart (Rs=–0.22, p<0.05), and malignancy damage (Rs=–0.18, p<0.05). Serological correlations for IL-17A existed with immunoglobulin G (IgG) levels (Rs=0.21, p<0.05), high sensitivity C-reactive protein (hs-CRP) levels (Rs=0.28, p<0.05), proteinuria (Rs=0.64, p<0.05), and pre-albumin (Rs=–0.22, p<0.05). Longitudinal data showed only modest fluctuation in IL-17A levels, independent of SLEDAI-2K.

Conclusion: These results suggest that IL-17A, while participating in inflammation, may also serve a protective purpose in SLE patients.

Keywords: IL-17A, Systemic Lupus Erythematosus, SLEDAI, organ damage

Introduction

Interleukin 17A (IL-17A) is the predominant cytokine of the interleukin 17 (IL-17) family (1, 2). In humans, IL-17A is primarily expressed by the T-helper-17 (Th17) subset of CD4+ T cells (2), but is also produced by neutrophils, natural killer (NK) cells, and CD8+ and double-negative (DN) T cells (3). Studies involving systemic lupus erythematosus (SLE) patients have reported increased numbers of Th17 cells in sera and in the biopsied tissue of individuals with kidney damage and lupus nephritis (LN) (4, 5). Increased IL-17A levels have also been reported in the sera of SLE patient subsets, particularly those with LN (4-6). Furthermore, in lupus-prone mice, the over-expression of IL-17A and subsequent expansion of DN T cells in the tubulointerstitial space has been linked to the development of nephritis (4, 7-11).

Interleukin 17A is a multifunctional cytokine that impacts neutrophil recruitment, mediating both T-helper-1 (Th1) and T-helper-2 (Th2) cytokine production, and it possesses angiogenic properties through apoptosis modulation (3, 12, 13). IL-17A production, in vivo and in vitro, is primarily controlled by transforming growth factor beta 1 (TGF-β1) and interleukin 6 (IL-6) via the activation of signal transducer and activator of transcription 3 (STAT-3) in mouse and human models, respectively (14-16). Under normal circumstances, IL-17A has the ability to recruit neutrophils to arrest tumor cells (2), whereas excessive IL-17A can contribute toward tumor growth by overcoming interferon gamma (IFN-γ) tumor surveillance properties (14, 17, 18). Similarly, excess interleukin 17F (IL-17F) can support tumor proliferation by increasing the local vessel growth (17, 19). Given IL-17’s pleiotropic nature, its role in the pathogenesis of human and experimental SLE may involve more than participating in site-specific inflammation alone (20). With the recent reports of IL-
17 inhibition in achieving clinical benefit in ankylosing spondylitis, questions will be raised regarding the potential to exploit IL-17 inhibition in SLE patients or certain symptomatic groups (21, 22). Therefore, the aim of this research was to investigate IL-17A levels, clinical and serological associations between SLE patients and healthy controls, as well as to determine the association of IL-17A levels with disease activity and organ damage within SLE patients.

Material and Methods

In a cross-sectional study design, we recruited 102 SLE patients, who fulfilled the relevant American College of Rheumatology’s classification criteria for SLE and had detailed clinical information and blood samples collected during an extended outpatient visit. A group of 31 healthy volunteers served as controls for serological measures. Disease activity was recorded using the Systemic Lupus Erythematosus Disease Activity Index-2K (SLEDAI-2K) and the Physician Global Disease Activity and Patient Global Disease Activity visual analogue scales (VAS).

Active disease is defined as having SLEDAI-2K scores of ≥3 (23). The Systemic Lupus International Collaborative Clinics (SLICC) Damage Index (SDI) was used to quantify overall and organ-specific damage (24). Overall, 69% patients used corticosteroids (prednisone) at a median dose of 3.75 mg per day (Table 1). Cardiovascular events were defined as a confirmed occurrence of myocardial infarction, thrombosis, or stroke. We included patients in our malignancy category when a solid or hematological cancer had developed. This included cancer(s) of the thyroid, vulva, cervical, lung, skin, and bladder, as well as leukemia or lymphoma.

Serology

Anti-double-stranded DNA (anti-dsDNA) and other autoantibody assays were performed at the clinical immunology laboratory by a validated ELISA (EliATM and VarelisA®; Phadia GmbH, Freiburg, Germany). IL-17A, B-cell-activating factor (BAFF), interleukin 1 beta (IL-1β), interleukin 4 (IL-4), IL-6, interleukin 10 (IL-10), interleukin 12 (IL-12), IFN-γ, macrophage inflammatory protein 1-alpha (MIP-1α), macrophage inflammatory protein 1-beta (MIP-1β), monocytic chemoattractant protein 1 (MCP-1), tumor necrosis factor-alpha (TNF-α), and transforming growth factor beta 1 (TGF-β1) were measured by a quantitative sandwich immunoassay (SuperArray ELISArrayTM kit; SuperArray Bioscience Corp., Frederick, MD, USA) with all the assays run in duplicate and the results, averaged. The manufacturer’s recommendations were followed throughout, and the same lot was used for each cytokine. For statistical purposes, values below the limit of detection (LOD) were replaced by the LOD value. The normal upper limit for the IL-17A cytokine was defined as the upper 95% percentile.

Statistical analysis

Results were presented with a measure of central tendency, i.e., median with inter-quartile range or mean with standard deviation or a count and percentage. Differences between groups assessed with the t-test, non-parametric Mann-Whitney U test, and chi-square test, wherever appropriate. The Rs. values were derived by using the Spearman r correlation test.

The longitudinal course of IL-17 levels was determined retrospectively for 18 SLE patients (n=18) with repeated measures of IL-17 prior to the baseline. This sub-cohort was similar in age, female predominance (86%), follow-up time, SLEDAI-2K, and both patient and physician Global Assessment of Disease Activity VAS values. However, the longitudinal cohort was more likely to have sustained organ damage (SDI), p<0.02. The comparison of the distribution of serial IL-17A results was analyzed non-parametrically by Friedman two-way analysis of variance by ranks. Statistical significance was set at α=0.05 or 5% level. The statistical analysis was performed on Statistical Package for the Social Sciences (SPSS) Version 22.0 (IBM Corp.; Armonk, NY, USA).

A principal component analysis (PCA) was performed using SPSS (Factor Analysis package) to determine the interplay of IL-17A amongst 33 serological parameters of the immune system (described in Table 2, 3) across various disease states of the 102 participants. Seven serological covariates were excluded due to missing data causing an inability of the PCA analysis to achieve convergence during an Oblimin rotation with Kaiser normalization. The final PCA iteration included 26 serological variables, as presented in Figure 1. It was found that the two first principal components, i.e., PC1 and PC2, accounted cumulatively for 49.74%, 46.51%, 50.12%, and 45.28% of SLICC-DI<1, SLICC-DI≥1, SLEDAI<3, and SLEDAI≥3, respectively.

Principal component analysis can illustrate the interplay of many parameters by optimizing the variance between the selected variables. In Figure 1 (SLEDAI-2K) and Figure 2 (SLICC-DI), the correlation amongst the variables is represented by the proximity of the vector points, i.e., the shorter the distance between two vector points, more similar.
### Table 2. Laboratory findings in SLE

<table>
<thead>
<tr>
<th>Serological Parameter</th>
<th>Controls</th>
<th>SLE patients</th>
<th>Independent Kruskall-Wallis Test (p)</th>
<th>Correlation with IL-17 (SLE serology only)</th>
<th>Correlation with high-IL 17 (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-17A (pg/mL)</td>
<td>28.4 (IQR 28.4, 88.33)</td>
<td>28.4 (IQR 28.4, 63.5)</td>
<td>0.948</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ESR (mm)</td>
<td>11 (IQR 4, 22)</td>
<td>20.0 (IQR 10.5, 33.5)</td>
<td>0.002</td>
<td>0.08</td>
<td>0.14</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>1.18 (IQR 0.65, 2.29)</td>
<td>2.1 (IQR 0.6, 5.0)</td>
<td>0.32</td>
<td>0.28**</td>
<td>0.22*</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>13.7 (IQR 12.75, 14.25)</td>
<td>13.1 (IQR 12.0, 14.1)</td>
<td>0.103</td>
<td>-0.15</td>
<td>-0.04</td>
</tr>
<tr>
<td>WBC</td>
<td>6.60 (IQR 4.90, 7.80)</td>
<td>5.8 (IQR 4.2, 7.1)</td>
<td>0.061</td>
<td>-0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>Platelets</td>
<td>265.5 (IQR 212.5, 330.0)</td>
<td>255.5 (IQR 212.0, 296.0)</td>
<td>0.338</td>
<td>-0.21*</td>
<td>-0.12</td>
</tr>
<tr>
<td>Albumin</td>
<td>45.5 (IQR 44.5, 46.5)</td>
<td>43.0 (IQR 41.0, 45.0)</td>
<td>&lt;0.001</td>
<td>-0.08</td>
<td>0.01</td>
</tr>
<tr>
<td>Pre-albumin</td>
<td>0.26 (IQR 0.23, 0.29)</td>
<td>0.3 (IQR 0.2, 0.3)</td>
<td>0.566</td>
<td>-0.22*</td>
<td>-0.19</td>
</tr>
<tr>
<td>Creatinine (umol/L)</td>
<td>62.0 (IQR 57.0, 67.0)</td>
<td>61.0 (IQR 52.0, 70.0)</td>
<td>0.748</td>
<td>0.02</td>
<td>0.08</td>
</tr>
<tr>
<td>IgG</td>
<td>12.3 (IQR 10.5, 13.0)</td>
<td>13.3 (IQR 10.9, 16.3)</td>
<td>0.041</td>
<td>0.21*</td>
<td>0.19</td>
</tr>
<tr>
<td>IgM</td>
<td>0.91 (IQR 0.71, 1.49)</td>
<td>0.95 (IQR 0.73, 1.46)</td>
<td>0.682</td>
<td>0.21*</td>
<td>0.19</td>
</tr>
<tr>
<td>Anti-dsDNA(IU)</td>
<td>0 (IQR 0, 0)</td>
<td>15.0 (IQR 0.0, 90.2)</td>
<td>-</td>
<td>-0.01</td>
<td>0.22*</td>
</tr>
<tr>
<td>C3 (mg/L)</td>
<td>1.13 (IQR 0.93, 1.34)</td>
<td>0.95 (IQR 0.80, 1.11)</td>
<td>0.009</td>
<td>0.11</td>
<td>0.04</td>
</tr>
<tr>
<td>Positive Coombs</td>
<td>0 (0%)</td>
<td>18 (20%)</td>
<td>0.26*</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>2.0 (IQR 2.0, 2.0)</td>
<td>1.3 (IQR 0.9, 1.8)</td>
<td>&lt;0.001</td>
<td>0.01</td>
<td>0.13</td>
</tr>
<tr>
<td>CD4-cells</td>
<td>0.99 (IQR 0.71, 1.26)</td>
<td>0.6 (IQR 0.4, 0.8)</td>
<td>&lt;0.001</td>
<td>-0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>B-cells</td>
<td>0.24 (IQR 0.19, 0.32)</td>
<td>0.10 (IQR 0.04, 0.22)</td>
<td>0.001</td>
<td>0.06</td>
<td>0.08</td>
</tr>
<tr>
<td>NK-cells</td>
<td>0.25 (IQR 0.21, 0.28)</td>
<td>0.10 (IQR 0.07, 0.17)</td>
<td>&lt;0.001</td>
<td>0.03</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Figures represent median values with interquartile range.

IL-17A: Interleukin 17 A; ESR: erythrocyte sedimentation rate; hs-CRP: high sensitivity C-reactive protein; WBC: white blood cells; IgG: immunoglobulin G; IgM: immunoglobulin M; Anti-dsDNA: anti-double-stranded DNA; C3: complement component 3; natural killer (NK) cells.

Numbers in the last two columns show Rs.

*Significantly associated with IL-17, p<0.05

**Significantly associated with IL-17, p<0.001

### Table 3. Cytokine interactions in SLE

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Controls</th>
<th>SLE patients</th>
<th>Independent Kruskall-Wallis Test (p)</th>
<th>Correlation with IL-17 (SLE serology only)</th>
<th>Correlation with high-IL 17 (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-17A (pg/mL)</td>
<td>28.40 (28.40, 88.33)</td>
<td>28.4 (IQR 28.4, 63.5)</td>
<td>0.948</td>
<td>-</td>
<td>0.43**</td>
</tr>
<tr>
<td>BAFF (pg/mL)</td>
<td>1.62 (IQR 1.13, 2.36)</td>
<td>1.7 (IQR 1.3, 2.3)</td>
<td>&lt;0.001</td>
<td>0.11</td>
<td>-0.08</td>
</tr>
<tr>
<td>IFN-γ (pg/mL)</td>
<td>43.79 (IQR 19.6, 119.34)</td>
<td>62.5 (IQR 19.6,134.1)</td>
<td>0.075</td>
<td>0.35**</td>
<td>0.38**</td>
</tr>
<tr>
<td>IL-1β (pg/mL)</td>
<td>17.90 (IQR 17.90, 348.08)</td>
<td>17.9 (IQR 17.9, 17.9)</td>
<td>&lt;0.001</td>
<td>0.54**</td>
<td>0.42**</td>
</tr>
<tr>
<td>IL-4 (pg/mL)</td>
<td>7 (IQR 7.0, 7.0)</td>
<td>7.0 (IQR 7.0, 7.0)</td>
<td>0.517</td>
<td>0.45**</td>
<td>0.39**</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>14 (IQR 14, 18.2)</td>
<td>14.0 (IQR 14.0, 19.5)</td>
<td>0.857</td>
<td>0.51**</td>
<td>0.29**</td>
</tr>
<tr>
<td>IL-10 (pg/mL)</td>
<td>5.90 (IQR 5.90, 23.64)</td>
<td>5.9 (IQR 5.9, 22.0)</td>
<td>0.598</td>
<td>0.49**</td>
<td>0.30**</td>
</tr>
<tr>
<td>IL-12 (pg/mL)</td>
<td>26.15 (IQR 12.6, 62.8)</td>
<td>24.6 (IQR 12.6, 61.7)</td>
<td>0.197</td>
<td>0.32**</td>
<td>0.32**</td>
</tr>
<tr>
<td>MCP-1 (pg/mL)</td>
<td>144.84 (IQR 82.4, 239.34)</td>
<td>133.7 (IQR 78.7, 219.8)</td>
<td>&lt;0.001</td>
<td>0.092</td>
<td>0.24*</td>
</tr>
<tr>
<td>MIP-1α (pg/mL)</td>
<td>-</td>
<td>15.0 (IQR 15.0, 103.5)</td>
<td>-</td>
<td>0.35**</td>
<td>0.25*</td>
</tr>
<tr>
<td>MIP-1β (pg/mL)</td>
<td>-</td>
<td>204.3 (IQR 161.2, 292.5)</td>
<td>-</td>
<td>0.30**</td>
<td>0.27**</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>-</td>
<td>34.3 (IQR 21.4, 87.4)</td>
<td>-</td>
<td>0.41**</td>
<td>0.34**</td>
</tr>
<tr>
<td>TGF-β1 (pg/mL)</td>
<td>-</td>
<td>592.3 (IQR 347.1, 859.7)</td>
<td>-</td>
<td>-0.01</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Figures represent median values with interquartile range.

Interleukins 4, 6, 10, 12, and 17A (IL-4). Interleukin-1β, B-cell-activating factor (BAFF), interferon gamma (IFN-γ), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1 alpha (MIP-1α), macrophage inflammatory protein 1 beta (MIP-1β), tumor necrosis factor alpha (TNF-α), and transforming growth factor beta 1 (TGF-β1).

Numbers in the last two columns show Rs.

*Significantly associated with IL-17, p<0.05

**Significantly associated with IL-17, p<0.001
is the influence of these two variables, or a cluster of variables, on the variance of the other variables in the PCA; further, the strength of the variables’ ability to influence the variance on other variables in the PCA is determined by the distance of the vector point from the origin.

Ethics
All the participants provided informed and written consents for the use of their anonymized data and samples collected as part of a protocol approved by the regional ethics committee (REC North 2015/1400).

Results
Descriptors
Systemic lupus erythematosus patients and controls were effectively matched for age (49 vs. 50 years, p>0.05) and gender (87% female vs. 77% male, p=0.009). SLE patients showed modest Global Disease Activity with a SLEDAI-2K score of 6 (IQR 2, 11), an average Physician VAS of 2.7±2.1, and average Patient VAS of 3.4±2.5 (Table 1). The disease activity was mostly related to migraines, arthritis, low complement levels, positive anti-dsDNA, rash, alopecia, and Raynaud’s phenomenon. The median SDI score was 1 (IQR 0, 2; range: 0–9) with the most frequent organ damage cited as being either musculoskeletal (21%), neurological (19%), heart (15%), or malignancy (13%). At the time of this study, 57% patients were taking hydroxychloroquine; 37%, immunosuppressive (IS) medication, i.e., azathioprine, mycophenolate, methotrexate, or cyclophosphamide; and 41%, some form of anticoagulant therapy.

Clinical associations for IL-17A
Median IL-17A levels were similar for SLE patients and controls (28.4 vs. 28.4 pg/mL, p=0.90). The use or dose of prednisolone was unrelated to IL-17A levels, nor were IL-17A levels influenced by the use of anti-malarial, IS, or anticoagulant therapies. IL-17A did not correlate with SLEDAI-2K, but was inversely associated with age (Rs.=–0.29, p<0.004), systolic blood pressure (Rs.=–0.31, p=0.002), and years of smoking (Rs.=–0.43, p=0.001). The IL-17A level did not correlate with the overall SDI, but was inversely related with cumulative heart damage (Rs.=–0.22, p=0.025) and a history of cancer (Rs.=–0.24, p=0.019).

Serological associations for IL-17A
IL-17A was correlated with high sensitivity C-reactive protein (hs-CRP) (Rs.=0.28, p=0.008), immunoglobulin G (IgG) (Rs.=0.21, p=0.049) and immunoglobulin M (IgM) (Rs.=0.21, p=0.066), and positive Coombs’ test (Rs.=0.26, p=0.015). IL-17A was inversely correlated with platelet count (Rs.=–0.21, p=0.034) and pre-albumin levels (Rs.=–0.22, p=0.03) (Table 2). IL-17A correlated with a range of pro-inflammatory cytokines including IL-6 (Rs.=0.51, p<0.001) (Table 2), but not with regulatory lupus cytokines, such as BAFF (Rs.=0.101), MCP-1 (Rs.=0.092), or TGF-β (Rs.=–0.098) (p>0.10 for all of them).

PCA of cytokine levels including IL-17A
In the PCA of a low disease activity state (SLEDAI-2k<3), the 1st principal component (PC1) included the cytokines IL-10, IL-4, IL-1β, TNF-α, IL-17, IFN-γ, MIP-1β, IL-12, MCP-1, and MIP-1α.
the x- and y-axes in Figure 2.

...moving beyond the –0.30 to 0.30 threshold on... decreased effect on the variation in the model by... not being correlated with the other variables... from the origin for SLICC-DI≥3. Despite BAFF... close to the origin for SLICC-DI<1, moving away... IL-17A was... in the PCA for SLICC≥1. Additionally, BAFF was... also modestly associated with lower damage scores for malignancy and heart conditions. These results suggest that in SLE, IL-17A could maintain its pleiotropic characteristics, under-taking a more complex role than simply orchestrating inflammation. There is experimental evidence regarding the... from studies in knockout mouse, where... less striking (11). A number of studies, mainly... IL-17A levels or the number of Th17 cells with... contribution to the development of renal immune deposits (25). The evidence for a role in the pathophysiology of human SLE...
Furthermore, IL-17A demonstrated an inverse correlation on cancer frequency in this SLE cohort. This protective effect was robust with a significant difference in the mean IL-17A level for those without and with a history of cancer (103 vs. 31 pg/ml). IL-17A has been described in various in vivo and in vitro models to possess both pro- and anti-tumor properties (2, 3). IL-17A, secreted by Th17 cells, can promote tumor growth through inducing vascular endothelial growth factor (VEGF) and increasing proangiogenic activity (17). The increased vasculature about the tumor provides more oxygen and nutrients, enabling its proliferation. On the other hand, IL-17A induces DC maturation, activation of macrophages, neutrophil recruitment, and NK cell and T-cell-induced cytosis; all of them contribute toward the destruction of tumor cells (2). Our study, therefore, adds an important clinical perspective, demonstrating that at levels similar to healthy controls, IL-17A possesses net anti-tumor functionality in SLE patients. However, further investigation is required to determine the circumstances and levels of IL-17A that would contribute toward such a state (2, 14, 18, 39).

There is a dearth of evidence regarding the long-term course of cytokines, including IL-17A, in SLE patients (40). Zickert et al. (5) showed that IL-17A levels were reduced 7 months after cyclophosphamide-based induction treatment for LN. In a random subset of patients in our cohort who did not receive induction treatment, longitudinal IL-17A levels did not fluctuate significantly over several years of observation. While an increase in cytokine levels over time in the general population has been described and considered to represent unhealthy aging due to underlying inflammatory processes (41), in a cohort of early arthritis patients, there was no significant change in IL-17A over a series of developmental stages (40).

The limitations of this study lie in the fact that our patients were all of Northern European descent and were mostly in a state of low disease activity, such that results cannot be extrapolated to cohorts with a different genetic or clinical makeup. Our results are based on clinical and serological findings and, therefore, cannot confirm the cellular source or causation of effects by IL-17A, for which further experimental studies will be needed. The strength of this study is the availability of a large range of disease characteristics in all the patients, the inclusion of longitudinal organ damage data, and the introduction of PCA to delineate the complexity of cytokine involvement in SLE.

In conclusion, IL-17A levels in this SLE cohort were similar to controls. IL-17A levels correlated with markers of inflammation including a range of other cytokines in SLE patients. While not clearly related to disease activity, IL-17A levels were inversely related to blood pressure, heart damage, and malignancy development. This dual role of IL-17A suggests that inhibiting pro-inflammatory IL-17 effects in SLE patients could have wider and significant clinical implications.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of North Norway (REC North 2015/1400).

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - JC; Design - WR, JC; Supervision - JC; GOE; Resources - JC, GOE; Materials - JC, GOE; Data Collection and/or Processing - GOE, JC; Analysis and/or Interpretation - WR, SG, JC, Literature Search - SSG, WR, JC; Writing Manuscript - WR, S., GOE, JC; Critical Review - WR, SG, GOE, JC.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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