N-Acetyl- galactosamine, the ligand of the hepatic asialo-glycoprotein receptors, conjugated to a synthetic siRNA. It targets and degrades a region of the SERPINC1 gene mRNA, preventing antithrombin production and enhancing thrombin generation. Antithrombin is a potent anticoagulant which inactivates FIXa, activated factor X (FXa) and activated factor II (FIIa/thrombin). Therefore, fitusiran can correct the coagulation imbalance and prevent the bleeding phenotype. Concizumab is an IgG4 monoclonal antibody targeting tissue factor pathway inhibitor (TFPI). It presents an alternative therapy for HA and HB patients, both with and without inhibitors. TFPI is a coagulation inhibitor. It limits coagulation during the initiation of the coagulation cascade through inhibition of the tissue factor-activated factor VII (TF-FVIIa) complex and through FXa inhibition. Gene therapy presents a novel and effective treatment modality for hemophilia, potentially bypassing complications of other therapies. Gene therapy regimens consist of single infusions of a viral vector, which result in transduction of a gene coding for the deficient factor into patient hepatocytes. Current gene therapy regimens for hemophilia predominantly utilise adeno-associated virus (AAV) vectors to deliver the required gene. **Conclusion:** Current factor replacement poses numerous issues, resulting in poor adherence and reduced QoL. Inhibitor development presents a key limitation to factor replacement. EHL products, emicizumab, fitusiran, and concizumab (summarised in appear effective in patients with and without inhibitors, and their longer half-lives enable less frequent injections.

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OPTIMIZATION OF FIXED DURATION TREATMENT OPTIONS IN CHRONIC LYMPHOCYTIC LEUKEMIA: CURRENT DATA AND FUTURE DIRECTIONS

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Introduction of Bruton tyrosine kinase inhibitors (BTKi) and B-cell lymphoma 2 (Bcl-2) antagonists changed the historical approach to chronic lymphocytic leukemia (CLL). Fixed-duration, targeted combination of these novel agents have replaced chemoimmunotherapy and have become preferred treatment options. Benefit of treating asymptomatic early stage disease is yet to be shown and indications for treatment are still mostly guided by International Working Group for CLL (iwCLL) 2018 recommendations. However; risk stratification has also come to question as genetic studies such as 17p/TP53 mutations, IGHV mutation status showed better risk analysis following chemoimmunoterapy (CIT) era. BTKi and Bcl-2 inhibitors also led to investigations on duration of treatment (fixed duration versus continuous) and best combination that provides most overall survival (OS) and progression-free survival (PFS) benefit. Since most CLL patients are elderly, comorbidities limit treatment options and these comorbidities correlate with shorter OS. Prior studies have shown that young and fit patients benefited from first line CIT such as fludarabine, cyclophosphamide, rituximab (FCR) and FCR provided long term remissions in previously untreated patients. Advent of BTKi and venetoclax offered a better treatment option for older population with high Cumulative Illness Rating Scale (CIRS) with fewer side effects although negative impact of comorbidities persisted.[3] In recent years, trials such as CLL14 have included patients with CIRS>6 and low creatinine clearence and showed the FD obinituzumab plus venetoclax combination was superior and provided longer PFS compared with to obinituzumab plus chlorambucil (median, 76.2 vs 36.4 months; hazard ratio [HR], 0.40; 95% confidence interval [CI], 0.31-0.52; $P < .0001$). Treatment with FD ibrutinib plus venetoclax in older patients also provided better responses. PFS was significantly longer for ibrutinib-venetoclax compared to chlorambucil-obinutuzumab (hazard ratio, 0.216; 95% confidence interval [CI], 0.131 to 0.357; P<0.001). PFS remained higher including patients 65 years of age or older or with a CIRS >6.These studies have provided basis for the approval of FD ibrutinib plus venetoclax combinations and showed clear benefit compared with historical CIT. FD treatments versus continuous ibrutinib became the focus of recent trials as well as determination of optimal duration for any treatment. Although continuous ibrutinib is the treatment of choice, trials have shown increased PFS and OS with FD treatments. With ibrutinib and venetoclax combination 36 −month overall survival (OS) was >95% regardless of high-risk features. Following recent trials, minimal residual disease (MRD) status as well as its incorporation into treatment duration emerged as a marker to guide CLL treatment. Subgroup analysis of trials have reported better PFS in patients with MRD negativity. Recently MRD guided treatment was shown to be effective and re-initiation of treatment with ibrutinib plus venetoclax was able to achive MRD negativity following discontinuation of treatment. Trials with ibrutinib and next generation BTKi and venetoclax are expected to incorporate MRD to further expand its role as an independent risk factor for long term survival. MRD tailored treatments in clinical practice may allow for discontinuation of treatment and also predict relapse. Appropriate method to determine MRD status requires further data from trials.

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OPTIMISATION OF THERAPEUTIC APPROACHES FOR HIGH-RISK ALL SUBTYPES

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There are actually several subtypes of acute lymphoblastic leukemia (ALL), some of which are especially difficult to manage. The high risk ALL subtypes included in this overview are neonatal ALL, KMT2A rearrangement, Philadelphia chromosome-positive (Ph+), Philadelphia-like (Ph-like), and Early T-cell precursor (ETP). Ph+ ALL: Tyrosine kinase inhibitors