Pan-African Journal of Health And Psychological Sciences
ISSN: 3093-4737 | www.pajhps.org
Vol.2, Issue 2 | April-June 2026

Revolutionizing Hepatic Disease Management: Emerging Biologics, Regenerative Strategies, and Next-Generation Antifibrotics in Liver Therapy and Diagnosis

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Abstract

Hepatic diseases constitute one of the leading health problems in the world, as they pose a significant morbidity and mortality rates, as they are progressive, and have few treatment options in their advanced phases. Other disorders which include metabolic dysfunction-associated steatohepatitis, hepatitis viral, cirrhosis, and hepatocellular carcinoma usually have no symptoms and are usually diagnosed at later stages when they become difficult to treat. The latest developments in biomedical studies have also brought new treatment methods that would alter the course of the disease instead of simply controlling the symptoms. More recent biologic agents are monoclonal antibodies, cytokine modulators, and gene-based interventions, which target molecular pathways of inflammation, impaired immune regulation and fibrosis, which are specific. Simultaneously, regenerative medicine including stem cell therapy, liver organoids and bioartificial liver systems have potential solutions to all aspects of hepatic reconstruction of structure and

ISSN: 3093-4737

functioning. Moreover, there is the development of next-generation antifibrotic agents such as HDAC inhibitor, RNA-based therapeutics, and novel small molecule to block fibrogenesis and induce fibrosis reversal. Improvement of non-invasive devices of diagnosis and imaging techniques also contribute to early diagnosis and individual treatment plans. Taken together, these advances point to a revolution of the integrated, regenerative and precision-based approach to the treatment of liver diseases

Keywords:
Hepatic disease, Biologic therapies, Regenerative medicine, Antifibrotic agents, Liver fibrosis.

1. Introduction

Hepatic disease can be described as a wide spectrum of liver disease that have a major clinical, economic and social impact on the global population [1]. Liver diseases impact on some of the vital functions such as metabolism, detoxification, protein synthesis and immune regulation, which in most cases, cause high morbidity and mortality when unattended [2]. Hepatic disease is a set of acute and chronic diseases, which include viruses (hepatitis B, C), alcohol abuse, metabolic dysfunction caused by obesity, drug poisoning and genetic factors, in the end result to fibrosis, cirrhosis and the most frequent type of liver malignancy, hepatocellular carcinoma [3]. Parenchymal and non-parenchymal cells of the liver, such as hepatocytes, stellate cells, Kupffer cells, and cholangiocytes, are important in pathogenesis and progression of disease [4]. Worldwide, approximately 2 million deaths are attributed to hepatic diseases representing a percentage of about 4 of all deaths, making it a significant cost burden to healthcare services and a significant social cost to many forms of hepatic disease [5]. End-stage liver diseases, including cirrhosis and liver cancer are the main causes of liver-related mortality; acute liver failure is not as prevalent but it kills quickly unless treatment is provided [6]. The emergence of innovative therapies, early diagnosis and preventive measures is urgent because of the recent rise in incidence in regards to obesity, diabetes, alcohol abuse and the adherence of viral hepatitis across the world [7]. Hepatic disease continues to be an important field of uncertainty in world health as

ISSN: 3093-4737

it is highly prevalent, progressive and extends widely in regard to patient well-being and healthcare services [8].

Liver disease is frequently non-specific in its early stage resulting in late diagnosis and worse prognoses [9]. The current biomarkers and images (ultrasound, CT, MRI) are not always sensitive and specific enough to early or subclinical disease detection, especially in non alcoholic fatty liver disease (NAFLD) and hepatocellular carcinoma [10]. Elaborate pathophysiology particularly when there is co-existence of metabolic or viral problems makes it difficult to determine disease progression and response to treatment [11]. End stage disease is optimally treated by liver transplantation which is limited by serious shortage of donors, high cost, immune rejection and possibly life threatening complications in the post-surgery period [12]. The more recent methods of cell therapy and organoid transplantation have potential, though they are still in early stages of development, and are hampered by engraftment problems, immune reaction, vascularization, nerve incorporation, and scalability to clinical applications [13].

The selection of the biologics, regenerative strategies, and the antifibrotics in the hepatic disease is due to the fact that these interventions involve the tissue and cellular regeneration mechanisms of liver injury, fibrosis, and organ failure [14]. These therapies offer possible disease-modifying, as opposed to symptom-management, possibilities with tissue repair and turning about of the pathogenic conditions [15].

Table 1: Key Hepatic Disease Types and Their Current Therapies

S.No.	Hepatic Disease Entity	Standard of Care Therapy	Emerging Strategies	Mechanistic Focus	Clinical Evidence/	References
3.	Metabolic Dysfunction-	Lifestyle intervention, pioglitazone,	GLP-1 receptor agonists (semaglutide)	Glucose/lipid metabolism, nuclear hormone	Semaglutide and resmetirom demonstrate	[10]

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	Associated Steatohepatitis (MASH, formerly NASH)	vitamin E	, THR-β agonists (resmetirom), FGF21 analogues, FXR agonists, ACC/PPAR modulators	receptor modulation	efficacy in fibrosis stage regression	
4.	Chronic Hepatitis B Virus Infection	Nucleos(t)ide analogues (entecavir, tenofovir), pegylated interferons	TAF, add-on sequential immunomodulation	HBV DNA polymerase, host immune response	Suppression rather than cure; evolving immunotherapeutics	[11]
5.	Chronic Hepatitis C Virus Infection	Direct-acting antivirals (DAAs: sofosbuvir, ledipasvir, glecaprevir/pibrentasvir)	Retreatment with alternative DAA regimens	NS3/4A, NS5A, NS5B inhibition	>95% cure rates, largely interferon-free protocols	[13]
6.	Autoimmune Hepatitis	Glucocorticoids (prednisolone/budesonide) ± azathioprine	Mycophenolate mofetil, calcineurin inhibitors,	Immune cell activation/inhibition		[8]

ISSN: 3093-4737

			biologicals (anti-CD20, TNF-α antagonists)		Biologic therapy for refractory/relapsing disease	
7.	Primary Biliary Cholangitis (PBC)	Ursodeoxycholic acid (UDCA)	Obeticholic acid, seladelpar (PPAR-δ agonist), bezafibrate	Bile acid pathways, FXR, PPARs	Seladelpar newly approved for pruritus-dominant PBC	[10]
8.	Primary Sclerosing Cholangitis (PSC)	Supportive (no approved medical therapy), UDCA (controversial), endoscopic therapy	Immunosuppression (experimental), anti-fibrotic/anti-IL17 therapies	Cholangiocyte biology, fibrogenesis, microbiota-immune axis	No disease-modifying therapy; clinical trial focus	[13]
9.	Hepatic Fibrosis and Cirrhosis	Etiology eradication (antivirals, metabolic control, alcohol abstinence)	Antifibrotic agents (F351, pirfenidone), cell and gene therapies, stem cell transplantation	Anti-fibrotic signaling, hepatic stellate cell modulation, regeneration	F351, a selective TGF-β/p38 inhibitor, in late-stage clinical trials	[6]

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10.	Acute-on-Chronic Liver Failure (ACLF)	Multidisciplinary supportive care, organ support	Plasma exchange, biologics, immunomodulation, cell therapy	Cytokine/ immune modulation, multiorgan support	Individualized, mechanism-based strategies emerging	[13]
11.	Hepatocellular Carcinoma (HCC)	Surgical resection, ablation, sorafenib or lenvatinib, immunotherapy (atezolizumab + bevacizumab)	TACE, systemic tyrosine kinase & immune checkpoint inhibitors	VEGF, PD-1/PD-L1, CTLA-4 axis, cellular proliferation	Immunotherapy and combination regimens improve outcomes	[10]

2. Emerging Biologic Therapies

2.1. Types of biologics: monoclonal antibodies, cytokine modulators, gene therapies

Biologics refer to a mixture of therapeutic products based on living organisms and monoclonal antibodies, cytokine modulators, and gene therapies [16]. Each type seeks the disease modification by different biological pathways and attacking specific pathways that are involved in different diseases such as cancer, autoimmune diseases and genetic disorders [17].

Monoclonal Antibodies: Monoclonal antibodies are molecules prepared in laboratories to bind to some antigens which in most instances are on the surface of cells e.g. cancerous cells or during an inflammatory process [18]. Common examples include: Rituximab vs. CD 20 (cancers of B-cells, autoimmune diseases) Abiater trastuzumab (Darrier) versus HER2 (breast cancer) [19]. TNF-alpha

ISSN: 3093-4737

(autoimmune diseases) anti-adalimumab and infliximab [20]. These antibodies can inhibit or neutralize an activity of its targets, they can also be used to destroy cells, or they can be used to deliver toxins directly to diseased cells [21].

Cytokine Modulators: Cytokine modulators refer to biologics that alter the signals of cytokines that are proteins that play a vital role in immune reactions and inflammation [22]. **Strategies include**: Removal of antibodies targeting proinflammatory cytokines (e.g., anti- TNF- a, anti- IL-6 receptor) Receptor inhibitors (e.g. recombinant IL-1 receptor antagonist, anakinra) Signaling-dependent cytokine receptors that are decoy receptors [23]. The agents have especially been essential in autoimmune and inflammatory ailments e.g. rheumatoid arthritis and psoriasis [24].

Gene therapies: This is the introduction, modification, or deletion of genetic material to a group of cells of a patient to treat or prevent an illness [25]. Methods include: Transferring workable gene to substitute damaged genes [26]. Modifying genes through such technologies as CRISPR [27]. Transfection of genetic constructs that cause the expression of therapeutic proteins or silencing of disease-causing genes [28]. Gene therapy is potentially curative, especially of genetic disorders as well as some rare diseases, because the underlying cause is at the DNA level [29].

2.2. Mechanisms of action in liver treatment

Metformin and other medications aid in the work of the liver by reducing the accumulation of fat and preventing the harm of the cells. This is achieved through alterations in the usage of energy by the cells and combating stress within the cell [30].

Minimize Inflammation: There are multiple therapies that relax the immune response of the body to ensure that it does not attack the liver [31]. This is useful in decreasing swelling and allowing the liver to heal [32].

Reduce Scar Tissue (Fibrosis): There are drugs that prevent the excess scar tissue produced by liver support cells known as stellate cells [33]. The reason why this is important is that scarring may obstruct normal hepatic functioning [33].

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Help Liver Regenerate: It is possible to regenerate the liver with healthy cells. Such medicines as well as some therapies and good nutrition stimulate the growth and healing of liver cells [34].When liver issues are due to such causes as viruses, high iron or similar causes, medications eliminate or block these causes, e.g. antiviral drugs used in hepatitis or chelators used in iron overload [35].

2.3. Clinical trial updates and latest breakthroughs

Cirrhosis Reversal in MASH: SYMMETRY Phase 2b trial demonstrated that efruxifermin (fibroblast growth factor analog) is able to reverse cirrhosis in steatohepatitis associated with metabolic dysfunction (MASH), enhancing fibrosis and metabolic health without adverse events [36].

Immunotherapy in Liver Cancer: CheckMate 9DW trial proved that nivolumab in combination with ipilimumab has considerable survival rates compared with lenvatinib or sorafenib in unresectable hepatocellular carcinoma (HCC), making it a useful first-line systemic therapy [37].

Functional Cure of Hepatitis B: The MARCH Phase 2 trial of the use of tabevibart and elebsiran combined with pegylated interferon demonstrated positive hepatitis B surface antigen seroclearance, which signified progress of a functional cure [38].

Thyroid Hormone Receptor Beta Agonists Resmetirom was FDA accelerated approved as the first agent in MASH with moderate to advanced fibrosis, to decrease hepatic fat and inflammation; an analog VK2809 is also demonstrating effectiveness in clinical trials [39].

Stem Cell Therapy: Mesenchymal stem cell therapies are increasingly popular as ways of enhancing the outcome of liver cirrhosis and studies are showing that they are safe and have potential clinical applications [40].

Combination Therapies: New combination Therapies are combination therapies of immunotherapy in combination with targeted treatments added onto conventional local therapies, which are extending the progression-free survival in liver cancers [41].

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Figure 1: Mechanisms of Biologic Agents in Liver Tissue

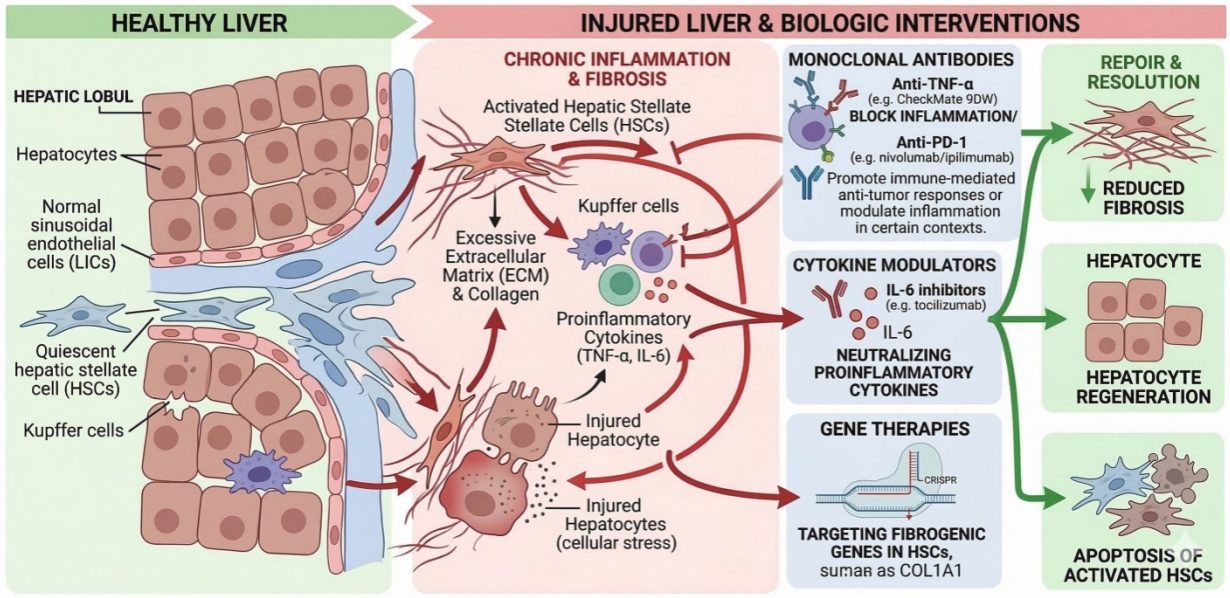

Figure 1: Mechanisms of Biologic Agents in Liver Tissue

Mechanisms of biologic agents in liver tissue: monoclonal antibodies (e.g., anti-TNF-α, nivolumab/ipilimumab), cytokine modulators, and gene therapies (e.g., CRISPR) targeting inflammation, HSC activation, fibrosis reduction, and hepatocyte regeneration pathways.

Table 2: Summary of Recent Clinical Trials on Biologics

S.No.	Biologic Agent	Indication	Trial Phase	Mechanism of Action	Key Clinical Outcomes	Adverse Events and Safety Profile	References
1.	Nivolumab + Ipilimumab	Advanced Hepatocellular	Phase 3	PD-1 and CTLA-4 immune	Improved overall survival,	Immune-related adverse events	[37]

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		Carcinoma		checkpoint blockade	objective response rates	manageable; no new safety signals	
2.	Belimumab	Autoimmune Hepatitis	Phase 2	B-cell activating factor (BAFF) inhibition	Reduction in ALT, IgG, improvement in histology	Mild infusion reactions; immunosuppression risks monitored	[41]
3.	Galactoarabinan-based biologic	Nonalcoholic Steatohepatitis	Phase 2	Anti-inflammatory cytokine modulation	Decreased inflammatory markers and fibrosis scores	Favorable safety, mild GI symptoms	[41]
4.	Anti-CCR2/ CCR5 Dual Antagonist	NASH with advanced fibrosis	Phase 3	Inhibition of monocyte/macrophage recruitment	Significant fibrosis regression, reduction in inflamma	Generally well tolerated; transient neutropenia reported	[39]

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5.	CTLA4-Ig fusion protein (Abatacept)	Autoimmune Hepatitis	Phase 2	T-cell costimulation blockade	Improved biochemical remission rates	Immunosuppression-related infections rare but recognized	[37]
6.	CAR T-cell Therapy (anti-FAP)	Hepatic fibrosis	Early phase 1	Elimination of activated fibroblasts	Preclinical success, ongoing human safety trials	Cytokine release syndrome mitigated via transient CAR expression	[40]
7.	Rilonacept	Primary Biliary Cholangitis	Phase 3	IL-1 blockade	Improvement in alkaline phosphatase and symptoms	Injection site reactions common; infection risk monitored	[37]
8.	Rituximab	Autoimmune Hepatitis (refractory)	Phase 3	Anti-CD20 B-cell depletion	Sustained biochemical and histologi	Increased risk of infections; infusion reactions	[41]

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3. Regenerative Strategies

3.1. Stem cell therapy (mesenchymal, hematopoietic, induced pluripotent)

The use of stem cell therapy as a treatment option of liver illnesses, in particular, hepatic fibrosis, cirrhosis, and acute liver failure, is promising [42]. Three important categories of stem cells such as mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), and induced pluripotent stem cells (iPSCs) have been extensively researched and are undergoing clinical studies [43].

Mesenchymal Stem Cells (MSCs) : The most common ones that have been widely researched in liver therapy are the MSCs because of their differentiation into hepatocyte-like cells and their regulatory of immune response [44]. They help in repairing liver by creating anti-fibrotic, anti-inflammatory, and anti-oxidative effects [45]. Clinical meta-analysis shows that MSC infusion of patients with acute-on-chronic liver failure produces significant positive outcome of liver functioning indicators (e.g., MELD score, albumin) but does not enhance the adverse effects [46]. Bone marrow, umbilical cord, and adipose tissue MSCs decrease fibrosis, increase hepatocyte regeneration, and improve ascites in cirrhotic patients. Nevertheless, standardized treatment regimens and long-term remaining effectiveness statistics are still required [47].

They have Hematopoietic Stem Cells(HSCs). HSCs promote the process of hepatic regeneration by fusing with hepatocytes and transforming the immune microenvironment rather than transforming into liver cells. They are not yet developed as MSC therapies nor have they been fully explored in this regard although potential [48].

The Induced Pluripotent Stem Cells (iPSCs). The fact that ipSCs could be hepatocyte like and person-specific could be able to generate better personal therapy. However, their use at that time

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is suppressed by the fact that they have their disadvantages such as safety, tumorigenicity and integration efficiency [49].

3.2. Bioartificial liver systems and organoids

The BAL systems are the extracorporeal systems that involve the combination of the live hepatocytes in the bioreacts which are designed to mimic the crucial liver processes of detoxification, metabolism, and biosynthesis [50]. Compared to the traditional non- bioartificial liver support, BAL provides metabolic activity, which is required in improving patient outcomes of acute and chronic liver failure [51]. The new developments are interested in the optimization of the sources of hepatocytes such as human-made hepatocytes (hiHeps) with fibroblasts, and the genetically modified porcine hepatocytes [52]. Indeed, hiHeps used in animal models as well as in the initial clinical trial showed high survival benefits of the Hepa Cure-BAL system [53]. It demonstrated safer and improved liver functioning in patients with acute-on-chronic liver failure who had a 90 percent survival at 28 days [54].

Liver organoids refer to miniature liver-like three-dimensional scaffolds, which are normally created by the use of stem cells such as induced pluripotent stem cells [55]. These liver organoids recapitulate the liver structure and functionality in drugs testing, disease modelling and transplantation experiments [55]. New inventions such as the UTO piA bioartificial liver system, a system based on gene edited organoids with immune suppression have been shown to last longer in preclinical liver failure models [56]. There will be a possibility of organoids to replace the lost liver functions and deal with inflammation [55].

3.3. Tissue engineering advances

The recent advances made in liver tissue engineering LTE have given a high hope of developing therapeutic alternatives to liver transplantation, in which case it plays an important role because of the shortage of donor organs [57]. The recent directions focus on biomaterials and 3D culture platforms, and cellular engineering so that the functional liver tissue can be reengineered in ex vivo [58].

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3.3.1 Biomaterials and Hydrogels:

Replacement of hydrogel usage has become significant scaffold in LTE due to biocompatibility of hydrogel and its ability to replicate extracellular matrix (ECM) of liver [59]. The nature of bio-polymer e.g. collagen, gelatin, hyaluronic acid and decellularized liver tissue hydrogel provides biochemical signaling to the he. patocytes, which is necessary to support survival, differentiation, and cellular functions [60]. Synthesis of synthetic polymers is also being achieved in order to achieve greater mechanical stability and customization. The versatile tunable hydrogels make possible the growth of organoids, liver-on-a-chip, bioprinted systems, and enhance basic research as well as preclinical studies [61].

3.3.2 The next two processes are known as 3D Cultivation and Bioprinting:

Cell culture systems, including 3D [3D] spheroids, organoids and bioprinted tissues, are a better representation of in vivo liver micro environments, compared to 2D cultures [62]. The advanced approach of bioprinting allows the spatial organization of any kind of liver cells (hepatocytes, stellate cells, endothelial cells) with precision, which allows cell-cell interactions, vascularization, and improved metabolism [63]. The liver-on-a-chip microfluidic platforms offer dynamic perfusing and real-time functional analyses that increase the physiological relevance of the microfluidic liver on-a-chip systems in disease modeling and drug discovery [64].

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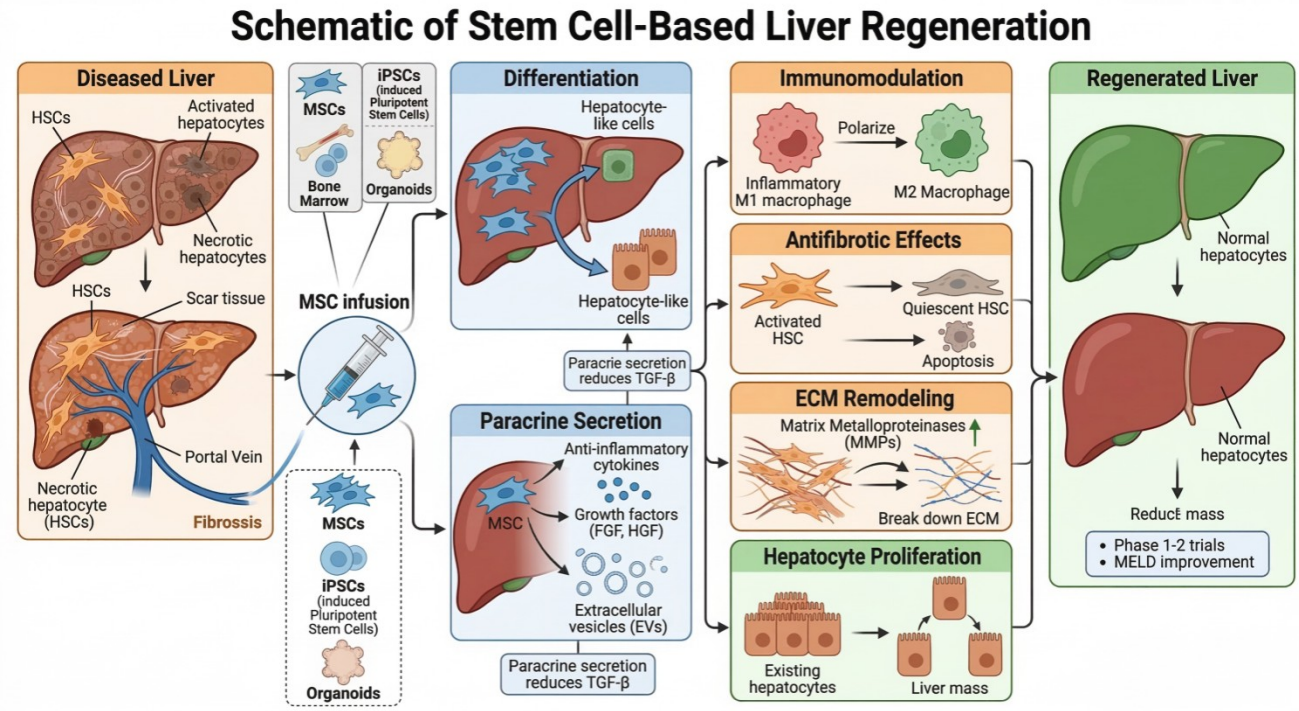

Figure 2: Schematic of Stem Cell-Based Liver Regeneration

Schematic of stem cell-based liver regeneration: MSCs from bone marrow/adipose tissue exerting paracrine effects for M2 macrophage polarization, HSC quiescence/apoptosis, MMP-mediated ECM remodeling, and enhanced hepatocyte proliferation in cirrhosis.

Table 3: Comparison of Regenerative Approaches

S.No.	Regenerative Modality	Mechanism of Action	Advantages	Limitations and Challenges	Clinical Status and Research Highlights	References
1.	Mesenchymal Stem Cells (MSCs)	Paracrine secretion of anti-inflammatory	Readily isolated from bone marrow, adipose tissue;	Variable engraftment, uncertain long-term	Phase 1–2 trials demonstrate safety	[43]

ISSN: 3093-4737

		cytokines, growth factors, immunomodulation, ECM remodeling	immunoprivileged; promote endogenous repair	safety, risk of fibrosis exacerbation in some contexts	and improved liver function; large-scale efficacy trials ongoing	
2.	Autologous Hepatocyte Transplant	Direct cell replacement to restore hepatocyte mass	Potential to restore liver function rapidly	Invasive cell harvesting, limited cell expansion, immune rejection risks	Experimental; success limited by availability of functional hepatocytes and logistics	[46]
3.	Induced Pluripotent Stem Cell (iPSC)-Derived Hepatocytes	Reprogramming of patient fibroblasts to hepatocyte-like cells	Unlimited source, patient-specific reducing rejection risks	Differentiation efficiency, tumorigenic potential, genomic instability remain concerns	Preclinical models showing functional engraftment; early phase human trials	[49]

ISSN: 3093-4737

					anticipated	
4.	Liver Organoids	3D mini-liver structures mimicking organ function	Advanced models for drug screening and regenerative transplantation	Complexity of manufacture, vascularization challenges	Primarily preclinical; promising for personalized medicine and disease modeling	[62]
5.	Macrophage-Mediated Therapy	Infusion of engineered macrophages to modulate inflammation and fibrosis resolution	Immunomodulatory; promote tissue repair and ECM degradation	Cell sourcing, functional heterogeneity, potential off-target effects	Phase 1 trials completed; evidence of fibrosis reduction in animal models	[63]
6.	Extracellular Vesicle-Based Therapy	Delivery of bioactive molecules via EVs from stem cells or hepatocytes	Cell-free, lower immunogenicity, targeted delivery potential	Standardization, dosing, scalability issues	Early phase trials ongoing; promising preclinical antifibrotic	[61]

ISSN: 3093-4737

					/ regenerative effects	
7.	Gene-Editing Approaches	CRISPR/Cas9 and other technologies to correct genetic defects or modulate fibrogenesis genes	Potentially curative, highly specific	Delivery challenges, off-target effects, ethical concerns	Preclinical development; clinical translation expected in next decade	

4: Next-Generation Antifibrotics

The next-generation antifibrotics are altering the treatment of hepatic disease by modulating the molecular causes of fibrosis reversal [65]. Hydronidone, kinase and TGF-b1-inhibit collagen synthesis, reverse the activation of hepatic stellate cells [66]. HDAC6- inhibitors drugs epigenetically re-program fibrotic genes [67]. TH Remodeling of scars and regeneration of hepatocytes with RNA-based therapies silence COL1A1 and HSP47 transcripts by ligand-tethered lipid nanoparticles [68]. These antifibrotics combine metabolic control, specific epigenetic repair, and regenerative communication, which allows the actual regression of fibrosis with enhanced safety and accuracy than previous small-molecule treatments [69].

4.1. Novel drug classes: HDAC inhibitors, RNA therapies, small molecules

The novel antifibrotic therapeutic development is now around three mechanistically distinct yet complementary classes; HDAC, RNA therapeutic, and next-generation small molecules- that

ISSN: 3093-4737

collectively redefine liver fibrosis treatment by epigenetic, transcriptomic, and molecular pathway- inhibition [70].

4.1.1. HDAC Inhibitors:

The other specific epigenetic therapeutic agent is histone deacetylase (HDAC) inhibitor which is used to inhibit fibrosis cellular engine (hepatic stellate cell, HSC) [71]. Preferential HDAC6 inhibitors (DR-3, FDR2) are active in the acetylation of a-tubulin and inhibition of TGF-b1/SMAD signaling to inhibit ECM deposition and myofibroblast proliferation [72]. Likewise, the class-I HDAC, LP340, inhibitor inhibits the oxidative stress and miR-23a which restores SnoN/Smad4 signaling to suppress fibrogenesis [73]. The antifibrotic effect of SAHA and Trichostatin A (TSA) is so high and pan-HDAC-inhibitors known to have a high probability of hepatotoxicity, which leads to the generation of isoform-selective HDAC6 and HDAC3 inhibitors to maximize safety benefits [74]. When used together, HDAC modulators have the potential to reverse epigenetic conditioning in a manner that would maintain the inactivity of HSC and reverse maladaptive chromatin states resulting in fibrosis development [71].

The new focus of novel antifibrotic drug development is on three mechanistically dissimilar, complementary classes- HDAC inhibitors, RNA therapies, and next-generation small molecules that are combined to redefine liver fibrosis therapy by repairing epigenetics, regulating transcriptomics, and inhibiting molecular pathways [75].

4.2.2. RNA Therapies: Antifibrotics based on RNA directly interfere with the genetic code of the fibrosis system by silencing or editing major fibrogenic transcripts [76]. COL1A1, TGF-b1, and HSP47 are silenced or edited by siRNA and miRNA mimics/inhibitors and prevent collagen production and stellate activation [77]. State-of-the-art ligand tethered lipid nanoparticles (LNPs) can now be delivered both cell-specifically by asialoglycoprotein (ASGPR) and PDGFRb receptors to decrease systemic inflammation and promote on-target fidelity [78]. Regeneration and metabolic recovery of hepatocytes are induced by therapeutic mRNAs, which include those that encode HNF4a and antifibrotic enzymes [79]. RNA therapeutics can provide a path to the

ISSN: 3093-4737

reversal of fibrosis as opposed to symptom suppression by combining transcript silencing with regenerative programming [80].

4.2.3. Antifibrotics Small molecules: The designed small molecule drugs are rationally designed and still form pharmacological mainstays because it is orally administered and multi-targeted in nature [81]. Hydronidone F351 inhibits the collagen synthesis by p38g kinase and TGF-b1 receptors, and fibrosis in chronic hepatitis B clinical trials is reported to be significantly reduced by F351 (Hydronidone) [82]. Drugs include PAI-1-inhibitor which independently regulate the remodelling of ECM, inflammation, and metabolic stress [83]. An interplay between these new classes of drugs is created through the epigenetic, signaling, and extracellular pathways, which is used to effectively prevent fibrogenesis, and to recover hepatic intrinsic repair pathways [84]. Combination of chromatin remodeling, gene silencing and planting control make the next-generation antifibrotics conclusive towards the actual hepatic regeneration and scar reversal [85].

4.3. Mechanisms targeting fibrosis development/reversal

4.3.1. Cellular Mechanisms :- HSC removal/apoptosis or inactivation: This is a form of regression which relies upon the deletion of activated HSCs via the process of apoptosis or by retreating to quiescence to stop production of collagen and fibronectin [86]. Half of activated HSCs inactivation promotes natural fibrosis regression Activation of anti-inflammatory (M2) macrophage polarization: Metalloproteinase discharged into milieu facilitates ECM breakdown and tissue remodelling Senescence of myofibroblasts: Senescent myofibroblasts release anti-fibrotic cytokines and matrix-breaking enzymes and alter the milieu to promote scar formation Myofibroblast polarization: Supporting ECM breakdown and tissue remodelling through encouraging [87].

4.3.2. Pathway-targeted and molecular approaches:- TGF-b/SMAD: TGF-b signaling is inhibited by antifibrotic and RNA therapy, which provokes the destruction of existing scar tissue

ISSN: 3093-4737

[88].ECM remodelling: The rise of the expression of matrix metalloproteinases (MMPs) and the suppression of tissue inhibitors (TIMPs) trigger the destruction of the existing scar tissue [89].

Immunomodulation: New immunotherapies, immunomodulators, and gene editing regimes suppress the immune system and inhibit inflammation and promote fibrolysis [90].

4.4. Preclinical and clinical advances

Preclinical pharmacology Precision-cut liver slices and Humanised organoid platforms have transformed the preclinical pharmacology [91]. The F351 phase 3 is a move in the correct direction to support an HDAC6 antifibrotic direct, which is statistically significant regression fibrosis staging and fibrosis-associating biomarkers, in steatohepatitis models [92]. The third is AI-directed repurposed compounds (Vorinostat, Panobinostat) which are subject to adaptive trials with the adaptive trial based on real-time organoid profiling [93]. Pro-C3, ELF score and liquid biopsy markers-based dynamic and noninvasive disease surveillance to redefine the field [94].

4.5. Safety and efficacy trends

Selectivity in the new antifibrotics becomes their distinguishing feature that substitutes the general fibrosis inhibition paradigm with selective modulation of microenvironment [95]. Compared to the first-generation pan-HDACIs; F351 does not induce severe alterations to the hepatic enzymes, and mRNA therapies are not related to the risk of inserting the genome using DNA-based vectors [96]. Safety strategies focus on: Minimizing parenchymal exposure: Cell specific nano – delivery [97]. Adaptive dosing patterns: Responsive to biomarker dynamics [98].Combinatorics-based regimens: Cleaner drug design and cumulative toxicity alleviation .Now, with the addition of AI analytics and omics biomarkers, toxicity can be predicted and, therefore, cleaner drug design and cumulative toxicity can be avoided [99].

Table 4: Recent Antifibrotic Agents—Mechanisms & Clinical Status

S.No.	Antifibrotic Agent	Mechanism of	Target	Clinical	Key	Reference

ISSN: 3093-4737

		Action	Pathway/Cellular Process	Development Stage	Clinical Findings and Notes	s
1.	F351 (Hydronidone)	Inhibition of p38γ MAPK and TGF-β1-mediated collagen synthesis	TGF-β signaling, myofibroblast activation	Phase 3	Significant fibrosis regression in HBV-associated liver disease; favorable safety profile	[92]
2.	Cenicriviroc (Dual CCR2/CCR5 Antagonist)	Blocks monocyte/macrophage recruitment and inflammation	Chemokine receptor signaling	Phase 3	Reduced inflammation and fibrosis progression in NASH; neutropenia observed in some patients	[97]
3.	Obeticholic Acid (OCA)	FXR agonist, reduces bile acid synthesis and inflammation	Farnesoid X receptor pathway	Approved (PBC), Phase 3 (NASH)	Improved fibrosis in PBC; mixed results in NASH with pruritus as common adverse effect	[92]
4.	Selonsertib	ASK1 inhibitor, reduces stress responses and apoptosis	Apoptosis signal-regulating kinase 1 (ASK1)	Phase 3 (discontinued for futility)	Failed to meet efficacy endpoints in Phase 3 NASH trials despite promising preclinical results	[93]

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5.	Pentoxifylline	Anti-inflammatory and antifibrotic via reduced TNF-α production	NF-κB pathway modulation	Off-label use/early trials	Benefits in fibrosis stabilization; variable clinical results	[93]
6.	Simtuzumab	Monoclonal antibody against lysyl oxidase-like 2 (LOXL2), inhibits collagen cross-linking	Extracellular matrix remodeling	Phase 2/3 (discontinued)	Lack of efficacy in clinical trials for fibrosis despite strong preclinical rationale	[97]
7.	Fuzheng Huayu (Traditional Chinese Medicine)	Multi-target effects including antioxidation, antifibrosis	Multiple (oxidative stress, HSC suppression)	Approved in China, Investigational elsewhere	Meta-analyses show improved hepatic inflammation and fibrosis markers	[98]
8.	RNAi Therapeutics (e.g., DCR-PHXC targeting HSP47)	Silencing fibrogenic gene transcripts via RNA interference	Collagen chaperone inhibition	Phase 1/2	Early human studies show reduction in collagen synthesis biomarkers	[89]

5: Integrated Approaches and Multimodal Therapy

Simultaneously by using multimodal combinations of small molecules, biologics, RNA therapies, and cell-based interventions, it is possible to target multiple pathways fibrogenesis, inflammation, metabolism, and regeneration in order to achieve integrated strategies to treat liver fibrosis [100]. Dual and triple regimens have scientific rationales such as FXR agonists, ACC

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inhibitors, and GLP-1 receptor agonists that may be combined to enhance hepatic histology and block collagen deposition and reverse hepatic functional impairment in NASH and fibrotic hepatic disease [101]. Microneedle arrays are also a new technology that can be applied to deliver cell-free stem cell secretome and nanozymes to fibrotic tissue, or combination cocktails can induce trans-differentiation of hepatic stellate cells and permit repair [102]. This integrative paradigm is important because it increases effectiveness and enhances clinical effects over monotherapy [103].

5.1. Synergy between biologics, regenerative medicine, and antifibrotics

This promotes radical effects on liver fibrosis through incorporating the specific molecular therapy, cell rehabilitation and remodelling [104].

Biologics, such as monoclonal antibodies and RNA therapy, block important fibrogenic pathways (e.g., TGF-b, CCR2/CCR5), hepatic stellate cell activation and inflammation [105].

Regenerative therapies which involves transplantation of stem cells and macrophages- activating paracrine signals that initiate the growth of hepatocytes, the inactivation of HSCs and liver architecture regeneration [106].

Antifibrotic small molecules (HDAC inhibitors, FXR agonists, FGF analogues) also destroy the extracellular matrix and the normal metabolism is restored [69]. They are additive or synergistic when applied as multimodal regimens, and thus bypasses the restrictions of monotherapy, and fibrosis reversal is quicker, safer and regenerates in a long-term manner [107].

5.2. Combined therapeutic models in current research

Integrated treatments of liver fibrosis are increasingly justified by the existing literature and it capitalizes on the interaction between drugs with complementing mechanisms metabolic modulators, anti-inflammatory drugs, anti-fibrotics and regenerative therapies [108]. Combination of FXR agonists with acetyl-CoA carboxylase inhibitors and GLP-1 receptor agonists experiences superior and more robust liver fat, fibrosis and biochemical reduction as compared to

ISSN: 3093-4737

monotherapy [109]. The other integrative strategies include the combinatoric strategies of utilizing small molecule cocktails of HSC activation, TGF-b, and EMT signaling with cell-based therapy or exosome delivery [110] . Multi-drug approaches in MASLD, NASH and viral hepatitis are in clinical trials and adaptive designs and biomarker-REA are being studied [111]. Besides fast fibrosis recovery and improved liver functioning, multimodal therapy also causes more safety and lower morbidity and increased clinical relevance, which means that the single-drug paradigm is transformed into the real integration and customized treatment [112].

5.3. Impact on personalized treatment and outcomes

Combined therapeutic models have significantly improved personalized treatment methods and clinical outcome in liver fibrosis [113]. Researchers find their regimens more effective than single-agent regimens by targeting the unique combination of metabolic, inflammatory, and fibrotic drivers in a patient with, e.g., the combination of FXR agonists, ACC inhibitors, and GLP-1 receptor agonists [114]. Such combinations do not only increase the fibrosis regression by targeting several pathways, but also contribute to the management and balancing of drugs side effects, e.g., semaglutide compensating hypertriglyceridemia caused by firsocostat [115]. In this context, practice of personalized medicine is based on the use of genomic, biochemical and imaging biomarkers to dictate therapy choice, dosage adjustment and continued observation [116]. History Multimodal therapy results in much improved histological and metabolic outcomes with clinicians being able to treat advanced disease and comorbidities, enhance safety profiles and attain lasting and patient centred remission of fibrosis-even in high-risk patients with cirrhosis or metabolic comorbidities [117].

ISSN: 3093-4737

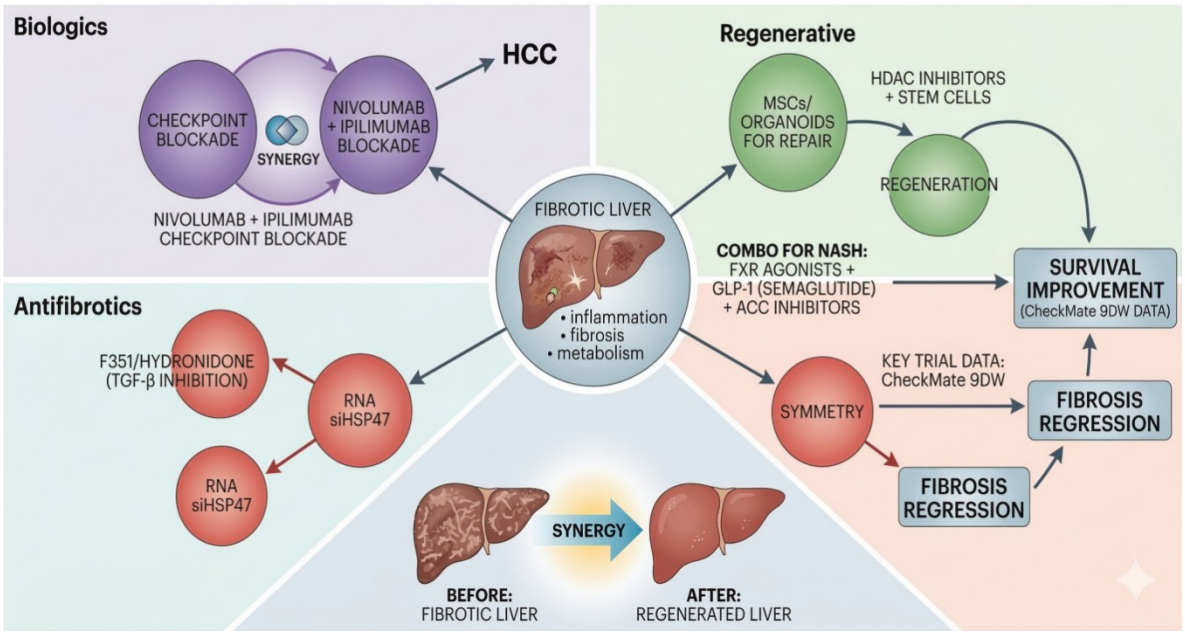

Figure 3: Combination Therapy Approaches in Hepatic Disease

Integrated multimodal therapy in hepatic fibrosis: synergistic combinations of biologics (checkpoint inhibitors), regenerative approaches (MSCs/organoids), and antifibrotics (F351, RNA therapeutics) reversing inflammation, fibrogenesis, and metabolic dysfunction (e.g., MASH, HBV).

6: Diagnostic Advances Accompanying Therapies

Advances in diagnostics that follow therapies have enhanced the management of liver diseases through the provision of safer, easier, and more accurate tools to detect and monitor diseases [118]. The blood tests have began to incorporate biomarkers such as liver enzymes (ALT, AST) and also some special markers such as microRNAs of extracellular vesicles which indicate the health status of liver cells and the level of fibrosis [119]. Transient elastography (FibroScan) and magnetic resonance elastography (MRE) are imaging techniques that carry out non-invasive measurement of liver stiffness to identify and stage fibrosis [120]. Such diagnostics will save the necessity of painful biopsies, identify diseases early enough, monitor treatment outcomes, and individualized therapy, which will positively influence patient outcomes and safety [2].

ISSN: 3093-4737

6.1. Non-invasive biomarkers (extracellular vesicles, blood-based markers)

Extracellular vesicles (EVs) refer to minute particles that are emitted by cellular units of the liver and contain microRNAs and proteins that demonstrate the health of the liver [121]. Applications of such EVs as non-invasive biomarkers to detect the presence of early liver disease, curing the progression and reaction of fibrosis are increasing. EVs have miR-122 and miR-192 that are strongly associated with liver inflammation and scarring [122]. Blood-based markers (e.g., liver enzymes (ALT, AST), collagen fragments and composite scores (e.g., FIB-4, ELF) and EVs could be used to diagnose and grade liver fibrosis [123]. They are quick, reusable, and non-invasive substitutes of liver biopsy, which allows to trace the disease in a more comprehensive manner and choose more personally regarding the therapy [124].

6.2. Imaging advancements (elastography, molecular imaging)

The new imaging techniques including the elastography and the molecular imaging technologies are changing the way the diagnosis and monitoring of the liver diseases is being done [125]. The ultrasound vibration-based measurement of liver stiffness, which is a fibrosis marker, is transient elastography (FibroScan), a noninvasive and fast test available at the bedside [126]. It is also widely applied to identify and grade fibrosis and cirrhosis in other liver diseases in order to prevent the application of invasive biopsy [127].

The increased accuracy of fibrosis assessment comes with shear wave elastography, which offers real-time images and focus point of evaluation [127].

The magnetic resonance elastography (MRE) is the combination of MRI and elastography sequences that creates detailed stiffness maps that may effectively detect fibrosis and give a comprehensive examination of the liver even in the presence of obesity or ascites [128]. Liver fat and inflammation is also measured using Molecular MRI biomarkers like cT1 and PDFF to improve the better response to treatment [129].

6.3. Impact of diagnostics on patient management

ISSN: 3093-4737

Biomarker panel and high-tech imaging are radically improving patient care. Algorithms based on FIB-4, ELF, and VCTE are beneficial in the triage process, decrease the needless specialist referrals, and direct assets to patients at the highest risk with up to 81% fewer needless referrals than previously practiced [130]. Serial elastography and EV-tracking enable longitudinal tracking, which is basically enhancing assessment of responses in the case of antiviral, antifibrotic or lifestyle interventions [131]. Individualized care advantages since clinicians will be able to profile the disease using blood and images, risk stratify, start therapy sooner, and adjust regimens in real time using quantitative feedback [2]. This does not only enhance efficacy but also reduces overtreatment, hospitalization and anxiety of patients, and enhances access in resource constrained environments due to simplicity, low cost and non-invasiveness of diagnostics.

7. Challenges, Limitations, and Future Perspective

There are significant regulatory, ethical and logistical issues in liver fibrosis therapy. Strict safety and efficacy data are needed by regulatory bodies on new antifibrotics; disparities in standards between regions and protracted trials are hurting access to patients . High-tech treatments, particularly, gene editing and stem cell procedures, stand under an ethical cloud because they can be risky and may require informed consent. High cost of drug development, poor diagnostic infrastructure and health disparities have a negative impact on its wider adoption logistically. The challenges in translation are caused by the disparities between the clinical and the animal models, the slow progression of the disease, and the lack of non-invasive endpoints. The future directions include the creation of multi-target therapies, scalable regenerative approaches, and digital capabilities to create more personalized and equitable care and even reverse fibrosis.

7.1. Regulatory, ethical, and logistical issues

The future of liver fibrosis treatment also has a consensus with the regulatory scrutiny that appears to be a major setback to the change and that the safety of the patients must be accorded the first priority. Antifibrotics (particularly biologic and gene-editing drugs) are the subject of years of efficacy

ISSN: 3093-4737

studies, which in many instances, may take years to get approved and develop at considerable expense. Another peculiarity connected with the ethical issues is stem cell cure and gene editing, as in this case, it is possible to mention the possible risk of immune rejection, off-target effect, and the inability to provide an informed consent to new procedures. Besides these, logistical problems are also present including high price of complex diagnostics and treatment, inadequacy of infrastructure in low and middle-income areas, and inequality in provision of health services that can impair their universal acceptance of these innovations. The aspects make it difficult to apply research discoveries in clinical practice.

7.2. Barriers to translation and patient access

Translational barriers between the laboratory and the bedside still exist. The pathology of the human liver is not necessarily completely recapitulated in the animal models, and patient etiological heterogeneity, comorbidity and genetic background complicate the design and efficacy assessment of clinical trials further. Long-term studies on sensitive and validated surrogate endpoints that are needed to follow hepatic fibrosis are gradual and lengthy, and some of them are still under development, withholding clinical implementation. Furthermore, the majority of the currently available treatment methods are focused on the stabilization, yet not reversal of fibrosis, which dictates the need to use a combination or multimodal approach to therapy. Globally, insufficient healthcare services, the cost of drugs and the unequal distribution of the population to the specialized care worsens the problem of access to patients, and fair access to the antifibrotic medications is an overwhelming task.

7.3. Future research directions and anticipated breakthroughs

Future research will address these difficulties by developing more effective non-invasive biomarkers and imaging modalities to diagnose at an early stage and monitor treatment in real-time to allow adaptive and personalized treatment. Repurposing and drug discovery via artificial intelligence can help in better discovering multi-target compounds and reducing toxicity and enhancing efficacy. Targets with better safety and tissue specificity by innovations are in the field of targeted delivery

ISSN: 3093-4737

systems, including ligand-directed nanoparticles and precision gene-editing. Engineered macrophages and stem cell derivatives are examples of cellular therapies, which are progressing to scalable clinical use, and which provide the regenerative solutions to fiber-like tissue replacement. The digital health platforms will be integrated to support precision medicine strategies, maximize adherence, monitoring, and outcomes . It is expected that effective multimodal antifibrotics with fibrosis reversal potential, scalable regenerative medicine, and access to high-technology therapies will be democratized. Taken together, these developments are promising a future in which liver fibrosis can be a chronic, progressive disease and be a curable one.

8. Conclusion

Hepatic diseases are a significant health-related concern in the world because of their growing number, theoretical pathophysiology, and high chances of developing fibrosis, cirrhosis, and hepatocellular carcinoma. The conventional management interventions mainly aim at managing the symptoms and reducing the speed of the disease; however, the new scientific developments have changed the current therapeutic situation and transformed it greatly. Monoclonal antibodies and cytokine modulators, and gene-based therapies are emerging biologic treatments that offer targeted therapies that control immune responses and critical molecular pathways responsible to liver injury and fibrosis. Simultaneously, mesenchymal stem cell therapy, liver organoids, and bioartificial liver systems are recent regenerative medicine approaches that have a potential in the restoration of hepatic functions and tissue regeneration. Innovations in the non-invasive diagnostics and imaging technologies also give way to earlier detection and monitoring of the disease and treatment planning that is personalized. Nevertheless, bio-logics, regenerative therapy and antifibrotic therapy integration is an exciting future approach to more effective, personalised, and possibly curative treatment of liver diseases despite the associated cost, accessibility, and long-term safety concerns.

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ISSN: 3093-4737

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