Balamurugan et al. Scr Med. 2026 Mar-Apr;57(2):389-404. DOI:10.5937/scriptamed57-60209

REVIEW ARTICLE

Emerging Biomaterial Strategies for Giant Cell Arteritis: Challenges and Future Outlook

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Abstract

Giant cell arteritis (GCA) is a common vasculitis of the big arteries that affects people as they get older and it usually results in potentially serious problems like vision loss and stroke. Steroids remain the cornerstone of GCA treatment, although long-term steroid use is associated with significant adverse effects and a high chance of recurrence. This review looked at biomaterials as a new treatment technique that could help improve GCA management through focused therapy, reduced systemic side effects and facilitated vascular restoration. A comprehensive evaluation of current breakthroughs in biomaterial-based GCA techniques was carried out, with an emphasis on nanoparticles, hydrogels and tissue-engineered scaffolds. The literature was reviewed to determine their therapeutic efficacy, biocompatibility and potential for clinical use. Biomaterials such as nanoparticles and hydrogels have showed promise in controlled drug delivery, allowing for focused treatment at sick artery sites while lowering systemic steroid exposure. Tissue-engineered scaffolds have shown promise for vascular repair and regeneration, at least more effectively than standard methods of treating an injured vessel. However, many problems exist, including maintaining long-term biocompatibility, stability and avoiding immunological responses. Although early preclinical studies have produced encouraging results, clinical translation is still in its infancy. Emerging biomaterials will be a potential area in GCA care, offering new opportunities for treatment efficacy enhancement while reducing side effects. Advanced research in the areas of biocompatibility and immune response challenges should be conducted to ease these promising tactics into clinical practice as a new hope for people suffering from this debilitating condition.

Key words: Giant cell arteritis; Biological products; Biocompatible materials; Drug delivery systems; Controlled drug delivery; Hydrogels.

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Citation:
Balamurugan BS, Sundaram VA, Marimuthu MMC, Anbalagan S, Chopra H. Emerging biomaterial strategies for giant cell arteritis: challenges and future outlooks. Scr Med. 2026 Mar-Apr;57(2):389-404.

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Received: 16 July 2025
Revision received: 29 August 2025
Accepted: 30 August 2025

Introduction

Giant cell arteritis (GCA) which is also called temporal arteritis is a type of chronic illness characterised by inflammation primarily of large and medium sized arteries including the temporal arteries.[1] It affects majority of older adults suffering from vasculitis with the possibility increasing in females aged over fifty years. In GCA, inflammation of arteries occurs which leads to tissue remodelling characterised by constriction and even occlusion of the blood vessels.[2] Several severe complications can also arise including permanent vision loss, paralysis and tissue death. For the last more than two decades now, scientists have tried to determine the role of immune system in bring-

ing about GCA which specifically focuses on T-cell and macrophage interaction with damaged arteries. These immune responses lead to surge in series of inflammation which comprise of cytokines, growth factors and proteases that result in damage of the blood vessels, loss of the endothelium as well as organs.[3] A blood vessel's cellular level GCA treatment at the moment relies significantly on corticosteroids with caution due to the risk of severe negative consequences. Biomaterials have great potential in treating GCA as they can target the particular area through controlled release of drugs while enhancing tissue regeneration. The three major classes of GCA biologics include nanoparticles, hydrogels and scaffolds.[4] Each of them has properties that enable them to meet the therapeutic needs in a particular manner.

Nanoparticles are ideal for drug transport because their sizes are in the nanometre range.[5] Nanocarriers are attractive due to their high surface volume ratio for drug loading. They can contain a variety of drugs, including drugs used in inflammation and release them at places of inflammation. Such an approach would make the drug more effective and reduce the adverse systemic effects. Hydrogels are composed of polymer networks which swell in water and possess high drug carrying capacity and allow controlled and sustained drug release at the inflamed tissue.[6] This reduces the need for drug administration more often and fosters good adherence by the patients and improves the treatment outcomes. Scaffolds are commonly used in the area of tissue engineering to promote vascularisation by inducing the growth of endothelial and smooth muscle cells to repair damaged blood.[7]

Biocompatibility, biodegradability, mechanical properties and specific biological interactions are some of the biomaterial's qualities for GCA treatment. The hostile environment due to inflammatory mediators is one of the key problems in the development of GCA biomaterials. Such an accomplishment will surely wish to create a material with less chances of stimulating immune response yet is effective for a couple of days. It would appear that the greatest potential lies in the application of nanotechnology in GCA therapy. There have been various classes of drug targeting nanoparticles to increase the drug effect and decrease side effects on nontarget tissues. For instance, sophisticated delivery systems can enhance the anti-inflammatory drugs' target to the inflamed arteries minimising the need for systematic steroids and their side effects. The other includes controllable bioactive ones which could be activated by various changes such as pH, temperature, or the presence of specific biomolecules. These materials enable targeted release of therapeutic agents at the site of inflammation and allow the adjustment of the dose and the time at which agents are released, thus more successful treatments with fewer side effects. Another sophisticated option is 3D bioprinting, which offers great potential for GCA treatment.[8] It provides cell-by-layer, biomaterial and growth factor-based deposition technology to precisely deposit layers, as well as extremely complex tissues capable of healing damaged blood vessels. Customisation of the biomaterial for the patient may now allow for more tailored GCA treatment.

In vitro research using cell cultures and tissue models has been extremely beneficial in understanding the interactions between biomaterials and inflammatory cells.[9] *In vivo* investigations using animal models have also produced promising findings, implying that biomaterials may be effective for reducing inflammation, improving vascular repair and obtaining favourable long-term outcomes. Although such preclinical findings are promising, the therapeutic potential of biomaterials for the treatment of GCA is yet to be tested and additional controlled human trials will have to demonstrate their safety and efficacy. Biomaterials' anti-inflammatory effect, in combination with biologics' capacity to modulate the immune response, could result in a more effective and more definitive therapy of GCA.[10] Such a treatment would address both inflammation and the ensuing immunological dysregulation that causes the disease.

Immunopathogenesis of GCA

GCA is a granulomatous vasculitis involving large- and medium-size arteries which shows a predilection for vessels encompassing the temporal and cranial vessels.[11] It is a disease whose pathology leads to a dysregulated immune response in precipitating vascular inflammation, remodelling and ischaemic disease. Its definitive aetiology is unknown although burgeoning evidence is indicative towards an innate- and adaptive-immunity partnership in initiating and maintaining arterial damage. Elucidation of such processes is critical since it forms the substratum for current immunosuppressive therapies as much as for

biomaterial therapies in their emergent stages. The early immune response in GCA is launched in the adventitia, where vascular dendritic cells (DCs) are sentinels.[12] These recognise signals of danger by pattern recognition receptors such as toll-like receptors (TLRs) in response to pathogen-associated (PAMPs) or damage-associated molecular patterns (DAMPs). On activation, DCs upregulate costimulatory molecules and produce pro-inflammatory mediators such as interleukin (IL)-6 and tumour necrosis factor alpha (TNF-α), recruiting innate immune cells towards the vascular wall.[13] Such an early recruitment allows for a later onset of chronic inflammation upon monocyte/macrophage activation.

Macrophages are key participants in pathogenesis in GCA. At sites within the arterial wall, they are differentiated into pro-inflammatory subtypes and in most instances merge into multinucleated giant cells, a histological signature for the disease.[14, 15] These cells produce matrix metalloproteinases (MMPs) degrading elastin and other extracellular matrix components, which compromise the vessel structure. Macrophages also produce reactive oxygen species (ROS) and inflammatory cytokines like IL-1β, IL-6 and TNF-α in greater measure, promoting tissue damage.[16] That leads to disruption of the arterial wall predisposing towards luminal constriction, ischaemia and severe morbidities like loss of vision or ischaemic stroke.

The adaptive immune system continues to support this inflammatory environment. Ag-pulsed DCs activate naïve CD4+ T cells, biasing differentiation towards Th1 and Th17 lineages.[17] Th1 cells produce interferon gamma (IFN-γ), which activates macrophages and drives granulomatous formation. Th17 cells produce IL-17, promoting neutrophil recruitment and chronic tissue inflammation. Concurrently, Tregs number and function are decreased, reducing their ability to engage in excessive immune suppression.[18] This imbalance in effector relative to Tregs is a key characteristic for GCA immunopathogenesis. Humoral immunity is also contributed by B cells. Activation of B cells results in the formation of autoantibodies directed towards vascular autoantigens like heat shock proteins. These autoantibodies can enhance endothelial dysfunction and vascular inflammation. B cells also produce cytokines IL-10 and TNF-α in addition to affecting T cell as well as macrophage activity. Combination of cellular as well as humoral immune responses results in perpetuation of inflammatory cycle leading to local as well as systemic manifestations.

These vascular manifestations of this dysregulated immune response are severe. When endothelial cells are exposed to inflammatory cytokines, they undergo apoptosis and detachment, which destroy barrier integrity and expose the subendothelial matrix. These processes initiate coagulation cascades, platelet activation and thrombosis, which further occlude vascular lumen. Concurrently, vascular smooth muscle cells (VSMCs) are transformed from a contractile state into a synthetic state.[19] Such a conversion up-regulates their production of extracellular matrix proteins and pro-fibrotic cytokines such as transforming growth factor beta (TGF-β), culminating in intimal hyperplasia and vascular fibrosis. These processes ultimately manifest over a period as structural remodelling, stiffening of vessels and ischaemic sequelae involving loss of vision, jaw claudication, stroke and aortic aneurysm.[20] Inflammation is not restricted to the vascular wall in GCA. Systemic symptoms are brought about by weight loss, fever and elevated acute-phase reactants such as CRP and ESR, which remain major diagnostic pointers. These systemic indicators are a sign of diffuse immune pathway activation in addition to chronic disease.

The pathogenesis of GCA can therefore be conceptualised as a multi-step model: activation within the adventitia of dendritic cells, recruitment/activation within granulomas of macrophages, Th1/Th17-directed expansion by adaptive responses with faulty regulatory control, contribution by B cells/autoantibodies and endothelial/smooth muscle dysfunction-mediated vascular remodelling.[21, 22] Altogether this multi-step model explains granulomatous inflammation/vascular damage typical for the disease. From a therapeutic perspective, such discoveries have guided corticosteroid use and biologic therapies like IL-6 receptor inhibitors. Vascular remodelling continues even in the presence of immunosuppression nonetheless reflects a need for novel approaches. Through a direct attack on the immune as well as structural aspects of disease pathogenesis, biomaterial therapies hold promise for a longer-lasting and less hazardous means to treat GCA. Figure 1 is a diagrammatic representation of immunopathogenic mechanisms in GCA, whereas Table 1 is representing major immune cell contribution, their cytokines, as well as drug targets.

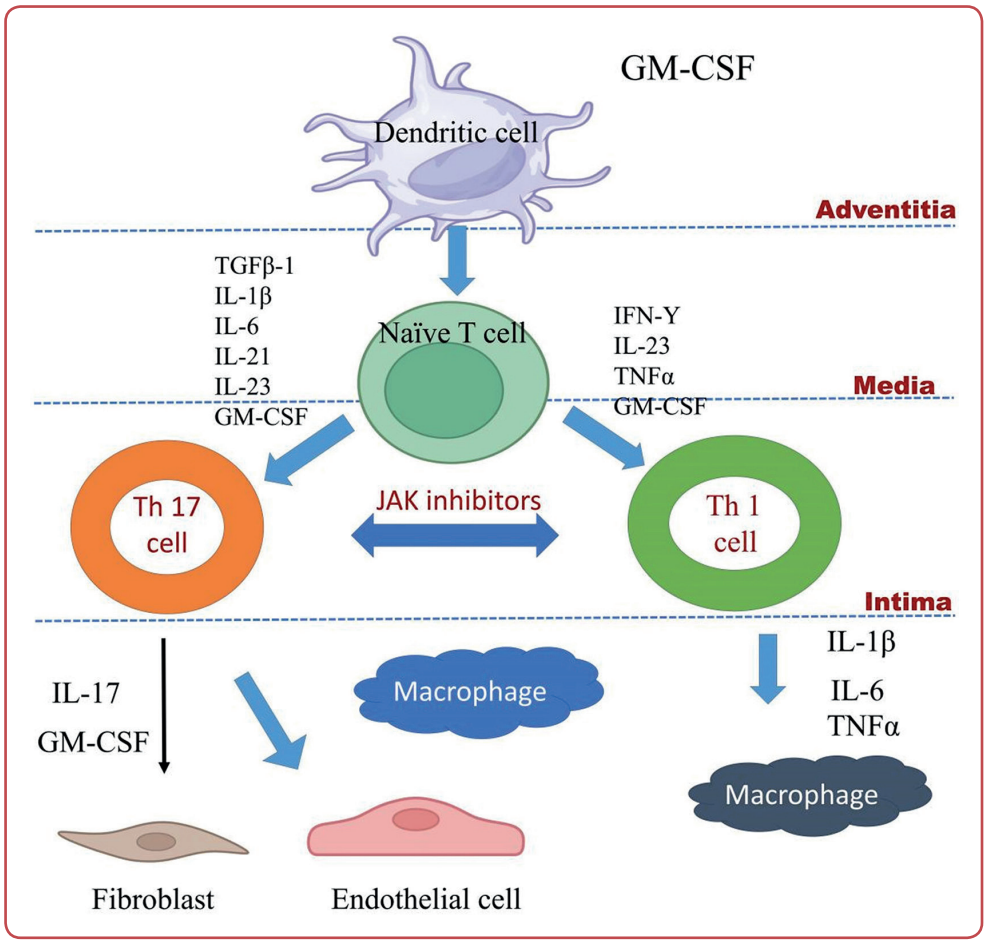

Figure 1: The pathogenesis of giant cell arteritis
IL: interleukin; TNF: tumour necrosis factor; TGF-β: transforming growth factor beta; GM-CSF: granulocyte-macrophage colony-stimulating factor: JAK: Janus kinase;

Table 1: Immune responses in giant cell arteritis (GCA) pathogenesis

N	Immune component	Role in GCA pathogenesis	Cytokines involved	Cellular interactions	Potential drug target	Ref.
1	**Dendritic cells**	Antigen presentation	IL-6, TNF-α	Activates T-cells	TLR pathway inhibitors	[23]
2	**CD4+ T-cells**	Chronic inflammation	IFN-ϒ, IL-17	Activates macrophages	IL-17 blockers	[24]
3	**Macrophages**	Granuloma formation	TNF-α, MMPs	Matrix degradation	MMP inhibitors	[25]
4	**B-cells**	Autoantibody production	IL-10, TNF-α	Autoantigen interaction	B-cell depleting agents	[26]
5	**Regulatory T-cells**	Suppression of immunity	TGF-β	Modulates inflammation	Treg activators	[27]
6	**Multinucleated giant cells**	Tissue destruction	MMPs	Extracellular matrix breakdown	TNF-α inhibitors	[28]
7	**Vascular smooth muscle cells**	Fibrosis	TGF-β	Phenotype switching	Fibrosis inhibitors	[29]
8	**Platelets**	Coagulation pathway	Thromboxane	Enhances vascular damage	Anti-thrombotic agents	[30]

IL: interleukin; TNF: tumour necrosis factor; MMPs: matrix metalloproteinases; TGF-β: transforming growth factor beta; TLR: Toll-like receptor;

Vascular inflammation and tissue damage

While immunological dysregulation causes giant cell arteritis (GCA), the clinical severity of the disease is mostly determined by its effects on vascular integrity and remodelling.[31] Once immune cells enter the arterial wall, continuous cytokine release and granulomatous activity set off a series of degenerative changes that gradually damage vascular structure and function. The loss of extracellular matrix (ECM) integrity is a critical component of the transition from inflammation to tissue damage.[32] Enzymes like matrix metalloproteinases destroy elastin and collagen, weakening the artery wall. This disturbance reduces vessel elasticity, resulting in stiffening and an increased tendency for aneurysm development. Endothelial cell death and detachment work together to undermine the vascular barrier, exposing the subendothelial matrix and triggering thrombogenic pathways.[33] The end outcome is a procoagulant milieu that promotes thrombus development and luminal blockage. Chronic oxidative stress compounds the harm. Reactive oxygen species produced inside the inflammatory milieu hasten endothelial aging, reduce nitric oxide bioavailability and maintain vascular dysfunction.[34] This oxidative burden not only exacerbates tissue injury but also inhibits the vessel's normal repair mechanisms, resulting in poor long-term consequences.[35] Another distinguishing feature of GCA disease is phenotypic flipping of vascular smooth muscle cells (VSMCs). Under inflammatory conditions, VSMCs switch from a contractile to a synthetic state.[36] In this synthetic phenotype, they create a lot of ECM proteins and pro-fibrotic cytokines, which cause intimal hyperplasia and vascular fibrosis. Such maladaptive remodelling narrows the artery lumen and inhibits blood flow, resulting in ischaemic consequences.

The clinical implications of these structural changes are considerable. Symptoms including jaw claudication, scalp discomfort and visual abnormalities are the result of localised vascular

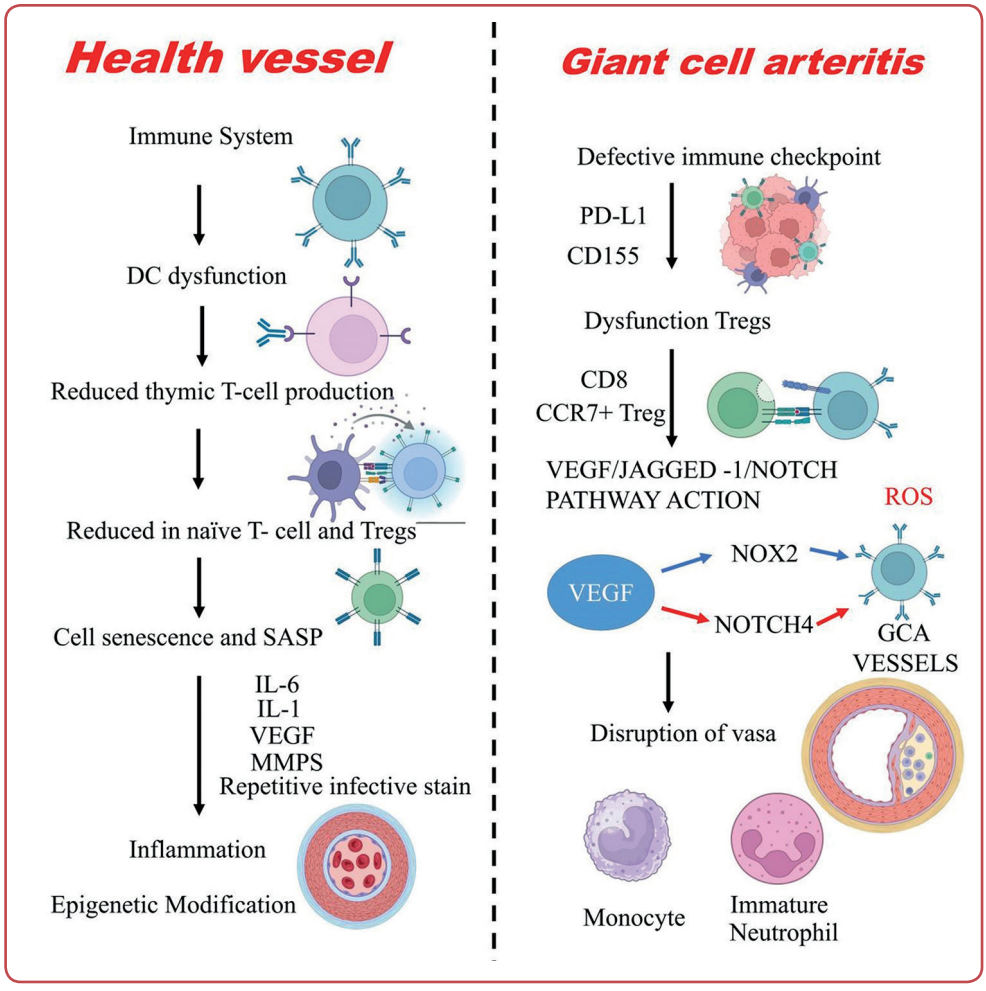

Figure 2: Schematic representation of vasculature disease activity and vascular remodelling

remodelling.[1] In advanced disease, structural weakening of major vessels such as the aorta predisposes patients to potentially fatal consequences such as aneurysm formation and arterial dissection.[37] These vascular sequelae are especially troubling since they might progress even in individuals undergoing immunosuppressive medication, implying that inflammation and tissue damage do not always heal simultaneously. The vascular pathology of GCA represents the damage to end-organ stage of immune-mediated inflammation. It links the previously identified cellular and molecular immunological pathways to the disease's observed clinical spectrum. Recognising this continuum highlights why therapeutic efforts must go beyond immunosuppression and include vascular healing, remodelling and long-term structural preservation. Figure 2 explains the vasculature disease activity and vascular remodelling.

Emerging biomaterials for GCA treatment

The development of biomaterials has transformed the treatment of inflammatory illnesses such as GCA, allowing for more targeted administration and efficacy. This review discusses the many biomaterials created for GCA therapy, including nanoparticles, hydrogels and scaffolds. These novel materials have emerged as important aids in the battle against vascular inflammation and tissue damage caused by GCA. Because nanoparticles are tiny and can functionalise their surface, they are employed to deliver drugs precisely without causing systemic side effects.[38]

Hydrogels have mechanical qualities that can be adjusted and their high-water content allows for continuous drug administration of medicinal medicines.[39] Such scaffolds serve as a scaffolding for structural restoration while also promoting vascular repair and regeneration. Biological interaction and material properties interaction is of significant interest in biomaterials design that is capable of restoring normal physiological function, repairing injured vascular tissue and treating inflammation.[40] The application of biomaterials in GCA treatment protocols has an immense potential to fill unmet therapeutic needs. It is essential to underscore from the very beginning that no biomaterial- or nanomaterial-based therapies have been evaluated in animal models of GCA to date. This signifies a significant limitation in the field, as the majority of existing data is derived from preclinical studies in related vascular disorders, including atherosclerosis, abdominal aortic aneurysm and vascular injury models. These conditions exhibit central characteristics akin to GCA—such as endothelial dysfunction, macrophage-driven inflammation, vascular smooth muscle cell remodelling and fibrosis—rendering them valuable surrogates for elucidating the potential mechanisms of biomaterials in GCA.[41] Evidence from these models indicates that nanoparticles can efficiently deliver anti-inflammatory agents to inflamed vessels, hydrogels facilitate sustained local release of biologics to injured arteries and biodegradable scaffolds encourage endothelial repair and vascular regeneration. While indirect, the insights show the translational potential of biomaterials for GCA, assuming adequate adaptation is carried out. Importantly, the immunological repercussions of biomaterial use must be carefully evaluated, as some are non-inert and may elicit inflammatory responses, while others can act tolerogenically.[42] Recognising the potential and limitations of these approaches provides a balanced foundation for discussing their future role in GCA therapy.

Biomaterials used include nanoparticles, hydrogels and scaffolds

Advanced biomaterials have revolutionised the therapies of inflammatory diseases such as GCA. It comprises nanoparticles, hydrogels and scaffolds, which possess new physical and chemical properties that enable direct drug delivery and tissue repair. Liposomes, polymeric nanoparticles and metallic nanostructures are some of the nanoparticle systems with incredible therapeutic potential with GCA.[43] These very small carriers, typically less than 200 nm in diameter, have the ability to deliver therapeutic drugs for controlled and sustained release, reducing systemic side effects.

Targeted nanoparticles can be designed to modulate specific inflammatory pathways, such as inhibiting pro-inflammatory cytokines, in an attempt to modulate directly the immunological dysregulation underlying GCA.[44] For instance, siRNA or anti-inflammatory drug encapsulation in nanoparticles decreased vascular inflammation and plaque progression in a model of atherosclerosis while endothelial repair in a model

of vascular injury was enhanced with polymeric nanoparticles.[45] These results indicate such therapies can be modified for vascular inflammation inhibition as well as for GCA-associated remodelling prevention in patients. Of the various nanomaterial platforms, PLGA nanoparticles, liposomes and naturally occurring polymers including chitosan and hyaluronic acid are best qualified for translational use in GCA.[46] These are FDA-approved or previously validated in clinical use in other inflammatory vascular settings with good safety, biocompatibility, as well as controlled degradability profiles. Metallic nanostructures, although favourable for high drug payloads, are more toxic for immunogenicity and also for longer-term accumulations and thus would be less ideal for first uses in GCA.[47]

From a therapeutic conjugate standpoint, the most logical candidates are medications which are already proved in GCA or other vasculitis. These are corticosteroids (to control local inflammation while suppressing systemic toxicity), biologics for IL-6 (eg tocilisumab) or TNF-α, or small-molecule inhibitors for JAK signalling, which act by modulating pathogenic T-cell as well as macrophage signalling.[48] Other newer approaches may involve anti-fibrotic agents (eg modulators for TGF-β pathway) or vascular sprout inducers as a means of vascular integrity restoration. Conjugating such therapies with bionanomaterials might allow for localised sustained delivery at the sites of arteries involved in inflammation while maximising efficacy while minimising systemic side effects.[49]

Another new class of biomaterials is hydrogels, which are three-dimensional networks of hydrophilic polymers. They are very biocompatible, biodegradable and mechanically tuneable, which makes them very suitable for extended drug delivery and targeted delivery in vascular tissue. Hydrogels can be loaded with anti-inflammatory drugs or biologics, such as monoclonal antibodies and bind to inflamed artery walls, circumventing vascular injury.[50] Stimuli-responsive hydrogels have been designed to maximise the specificity of GCA therapy, which may release cargo in response to environmental stimuli such as pH and temperature.[51] Biodegradable scaffolds are underlying structures for vasculature repair and regeneration. They give structural support to injured arteries, which is conducive to cellular infiltration, angiogenesis and extracellular matrix deposition. The most used types of scaffolds are PLGA- and collagen-based, which degrade into non-toxic byproducts while facilitating repair.[52] Such scaffold design innovations include the incorporation of growth factors or vascular endothelial cells, which maximises regeneration and enables restitution of impaired vasculature integrity due to GCA.[53] Introduction of these biomaterials into GCA treatment provides a multivariant approach to inflammation and tissue damage. Advances in nanotechnology, polymer science and biomaterial engineering are improving the efficacy and design of these systems and paving the way for more potent and personalised GCA treatments. This cross-disciplinary approach has the potential to restrict the burden of this chronic inflammatory disease and improve patient outcomes.

Table 2 outlines some biomaterial therapies, such as nanoparticles, hydrogels and scaffolds and their primary mechanisms of action, clinical status and advantages. These innovative approaches aim to improve treatment outcomes by enabling targeted drug delivery, sustained release and vascular regeneration. Although their promise, nanoparticles are not biologically inert. Some polymeric or metallic nanostructures are capable of activating complement pathways, producing oxidative stress, or eliciting foreign body reactions, which can exacerbate vascular inflammation.[63] Surface modification should thus be

Table 2: Advanced biomaterial-based therapies for giant cell arteritis (GCA)

N	Therapy type	Biomaterial used	Key mechanism	Clinical status	Advantages	Ref.
1	**Nanoparticle therapy**	PLGA nanoparticles	Targeted drug delivery	Preclinical	Reduced systemic side effects	[54]
2	**Hydrogel therapy**	PEG hydrogels	Sustained drug release	Preclinical	Improved patient compliance	[55]
3	**Biodegradable scaffolds**	Collagen, PCL scaffolds	Vascular regeneration	Preclinical	Promotes tissue repair	[56]

4	**Liposomal therapy**	Liposomes	Encapsulation of drugs	Preclinical	Enhanced drug bioavailability	[57]
5	**Smart biomaterials**	pH-sensitive hydrogels	Triggered drug release	Experimental	Controlled drug administration	[58]
6	**Gold nanoparticles**	Gold-based nanoparticles	Anti-inflammatory effects	Experimental	High drug-loading capacity	[59]
7	**3D bioprinted scaffolds**	Customised polymers	Vascular structure repair	Experimental	Tailored patient-specific therapy	[60]
8	**Solid lipid nanoparticles**	Lipid nanostructures	Anti-inflammatory delivery	Preclinical	Long-term stability	[61]
9	**Hybrid biomaterials**	Composite nanostructures	Multifunctional delivery	Experimental	Combines multiple advantages	[62]

carefully undertaken, accompanied by biocompatibility testing, in order to mitigate unwanted immune activation. Concurrently, nanoparticle platforms themselves can be designed with tolerogenic coatings or immunomodulatory cargos in mind, providing avenues for rebalancing immune responses in GCA.

Criteria for biomaterial selection in inflammatory diseases

The selection of biomaterials for therapy in inflammatory illnesses such as giant cell arteritis is critical for achieving efficacy and safety while being biocompatible and compatible with the biological environment.[64] Biomaterials must be highly biocompatible to avoid triggering unfavourable immune reactions. They must not aggravate inflammatory reactions in patients who are already suffering from autoimmune illnesses such as GCA. Materials with PEG-based polymers and naturally generated hydrogels (such as alginate or hyaluronic acid) are preferred due to their inertness and low immunogenicity.[65] Biomaterials for inflammatory illnesses should disintegrate in a regulated manner, allowing therapeutic chemicals to be released gradually while reducing the possibility of residual toxicity. Polymers such as poly(lactic-co-glycolic acid) (PLGA) are widely employed due to their customisable degradation patterns and FDA approval for clinical application.[66]

Biomaterials should efficiently encapsulate anti-inflammatory medicines, biologics, or gene-editing tools and provide sustained or regulated administration throughout time. When therapeutic levels gradually drop, these would produce longer-lasting effects with fewer negative effects. Hydrogels and nanoparticles are the most effective material systems because they can optimise drug loading and release kinetics.[67] The incorporation of targeting ligands, such as antibodies and peptides, into biomaterials improves the biomaterial's ability to localise therapeutic effects at inflamed vascular sites in GCA. Nanoparticles functionalised with vascular adhesion molecules or integrin-binding domains specifically target inflammatory lesions, reducing off-target effects.[68] Some applications, such as vascular restoration, will require biomaterials to have mechanical characteristics and elasticity that closely resemble biological tissue. Biodegradable scaffolds, in particular, should promote tissue regeneration while maintaining structural integrity under normal physiological circumstances. Biomaterials must be scalable and meet regulatory requirements for clinical translation. Materials with well-established safety profiles and track records, such as PLGA and collagen-based hydrogels, are more likely to receive regulatory approval. These criteria will allow biomaterials to play a revolutionary role in developing therapeutics for inflammatory disorders such as GCA.

Anti-inflammatory drug delivery systems

One of the key goals in treating GCA is to efficiently transport anti-inflammatory medications to the site of inflammation while minimising systemic side effects and increasing therapeutic efficacy.[69] Some studies have been conducted on the use of nanoparticles, liposomes and micelles in controlled drug transport and release to battle the disease. Nanoparticles, particularly bio-

degradable polymers, have sparked widespread attention because they can encapsulate hydrophobic medicines, protecting them from degradation and directing their release to specific areas.[70] This is an excellent example of PLGA nanoparticles being released directly at the inflammatory site, which may allow patients to reduce their dosage while increasing therapy compliance. Furthermore, surface modifications of nanoparticles allow them to target endothelial cells or immune cells implicated in the pathophysiology of GCA, ensuring that the therapeutic substance is administered precisely where it is required.[71] A second method of delivering anti-inflammatory drugs is through the use of liposomes, which are lipid vesicles. Liposomes are able to encapsulate lipophilic as well as hydrophilic drugs and this improves bioavailability by prolonging their circulation time in the bloodstream.[72] Targeting ligands may also be conjugated to the surface of liposomes, delivering them to the inflamed vasculature and minimising off-target toxicity and maximising overall therapeutic effects.

Biodegradable scaffolds for vascular repair

GCA causes permanent injury to the vascular wall, including weakening, scarring and loss of elastic recoil. Biodegradable scaffolds are one such solution to vascular repair and regeneration as they restore the structural integrity of damaged blood vessels.[73] Scaffolds are typically constructed from biocompatible and biodegradable materials like collagen, fibrin, or synthetic polymers like PLGA and polycaprolactone (PCL). Scaffolds not only provide a temporary structural support, but may even be preloaded with anti-inflammatory drugs or growth factors to promote the regeneration of tissue.[74] Upon failure of the scaffold, it is gradually replaced by host tissue, resulting in more effective healing with decreased risk of restenosis. Additionally, the biodegradable scaffold eliminates the necessity for surgical removal, a characteristic that is of incalculable value in the treatment of chronic disease like GCA and the vascular injury caused by such a disease.[75] Such scaffolds can be made to possess similar mechanical properties as vascular tissue, but yet provide adequate support without obstructing blood flow.

Biodegradable scaffolds provide support to compromised arteries and can be designed for release of anti-inflammatory or pro-regenerative factors.[76] Although scaffolds are not yet tested in GCA, evidence from aneurysm repair as well as atherosclerotic vascular disease models demonstrates their therapeutic potential. Collagen- and PLGA-based scaffolds seeded with vascular smooth muscle cells or endothelial progenitors were found to induce vascular regeneration while restoring arterial compliance.[77] Addition of growth factors like VEGF or PDGF increased further neovascularisation and remodelling. These results indicate that such scaffold systems would also be tailored for GCA, in which chronic inflammation and tissue destruction destroy vascular integrity. Advances in the field of material science, like the use of elastomers and nanocomposites, improve the strength and elasticity of such scaffolds, making them a suitable choice for large vessels involved by GCA.[78] Synthetic scaffolds, particularly those composed of synthetic polymers or composites, can evoke foreign body responses, activation of macrophages, or fibrotic encapsulation with resultant vascular compromise.[79] To prevent such risks, surface functionalisation and the use of biodegradable polymers derived naturally can improve immune compatibility. Of note, certain scaffold systems proved tolerogenic in as much as allowing immune regulation along with positive tissue remodelling, implying a bidirectional potential which needs to be delicately weighted in applications for GCA.[80]

Hydrogel-based therapeutics for continuous drug release

Hydrogels may be synthesised using natural polymers like collagen or hyaluronic acid, or using synthetic polymers like PEG. Hydrogels possess a gel-like structure which can encapsulate drug, growth factors and cells. A drug delivery system based on hydrogel possesses one more benefit in targeted delivery of the drug over the long time period necessary to decrease inflammation by sustaining therapeutically effective drug concentrations in the inflamed tissues. Anti-inflammatory drugs released from the hydrogel can be triggered by temperature, pH variations, or enzyme activity, directing the medicine to the exact location where it should be released.[81] This capacity to manage drug release improves therapeutic outcomes while also lowering the likelihood of negative effects associated with frequent pharmacological doses. Furthermore, hydrogels can be created to aid in tissue repair by promoting cell migration and proliferation. Hydrogels are appropriate components in vascular tissue engineering procedures due to their biocompatibility and ease of modification.

Hydrogel-based drug delivery systems are also being investigated for their possible application in combination therapies, where numerous therapeutic agents, such as anti-inflammatory medicines and growth factors, can be administered simultaneously to induce vascular regeneration.[82] For example, application of PEG-based hydrogels releasing IL-10 decreased neointimal hyperplasia following vascular injury while drug-loaded anti-inflammatory hyaluronic acid hydrogels promoted vascular healing in an aneurysm model.[83] These results indicate hydrogels as a versatile delivery system which might be developed for local administration of corticosteroids or biologics in inflamed arteries in GCA with reduced systemic toxicity and improved patient result. These biomaterials not only serve to address the requirement for focused and sustained drug administration, but they also open up new routes for vascular regeneration, making them critical components of upcoming GCA treatments. While hydrogels are generally regarded as biocompatible materials, some formulations remain capable of eliciting an immune response or local fibrosis depending on polymer type and degradable material.[84] Natural-source hydrogels such as hyaluronic acid and collagen, in contrast, were shown in vascular constructs to exert tolerogenic and anti-inflammatory activity in favour of immune regulation and tissue repair. Extending such functionalities while avoiding immunogenic formulations shall become critical for hydrogel-based therapies in GCA.

Advancements in biomaterial design for GCA

GCA must be treated using new ways that address both inflammation and vascular damage, which define the condition. The latest advances in the biomaterials engineering field have targeted the creation of materials that, besides inhibiting inflammation, also improve vascular healing. These advances have triggered interest in a variety of new strategies, such as those involving the utilisation of nanotechnology, smart biomaterials and 3D bioprinting.

Nanotechnology-based approaches to targeted therapy

Nanotechnology has great potential in the treatment of GCA in that it allows for personalised therapy at the cellular level. Nanoparticles, such as liposomes, polymeric nanoparticles and solid lipid nanoparticles, can be utilised for the delivery of anti-inflammatory drugs to the inflamed site directly, reducing systemic side effects and maximising drug efficacy.[85] The nanoparticles can be functionalised with high specificity of ligands for inflammatory markers found in GCA and deliver therapeutic drugs to the inflamed walls of arteries directly.[86] Another significant aspect is that nanoparticles are extremely small in size and thus they can penetrate deeper into tissue. This allows them to travel closer to the underlying cellular structures, improving the efficacy of contact. Targeting minimises the need for high doses and maximises therapeutic actions and thus nanotechnology is a highly promising mode of treatment for GCA.

Smart biomaterials are a highly promising development in the design of GCA therapeutic systems.[87] These materials are encapsulated with specific environmental stimuli, such as pH change, temperature change, or inflammation and release therapeutic payloads in a controlled, continuous manner. For GCA, such smart biomaterials can be created to release anti-inflammatory drugs directly to the site of vascular inflammation, with a desired release profile corresponding to disease progression. For example, pH-sensitive hydrogels or polymers can be utilised to release drugs in response to the acidic microenvironment found in inflamed tissues.[88] These materials not only improve the efficacy of therapy, but also decrease the frequency of administration, resulting in improved patient compliance. By integrating responsive elements into biomaterials, treatment can be dynamically optimised to the patient, resulting in improved therapeutic success.

3D bioprinting is the latest technology in the fabrication of scaffold templates with personalised patterning to treat vascular regeneration.[89] In reality, with the precise and controlled delivery of biomaterials, 3D bioprinting can deliver structures such as the intricate geometrical structure of blood arteries, thus becoming highly relevant for the repair and regeneration of damaged vascular tissues in GCA.[90] Such bioprinted scaffolds can be loaded with growth hormones, anti-inflammatory medication, or cells to assist in the healing and regeneration of tissues. Additionally, 3D printing can enable personalisation of therapy by designing scaffolds based on the anatomical needs of various patients. This means that the 3D-bioprinted scaffold in the case of GCA will serve as a replacement or an augmentation

of damaged vascular systems, simplifying the repair process and preventing some long-term impairments, for example, aneurysms or rupture of an artery. This approach, therefore, has tremendous potential for the establishment of vascular regenerative medicine because it ensures that there are more efficient and personalised means of treating GCA patients. The combination of these sophisticated biomaterial designs—nanotechnology, smart biomaterials and 3D bioprinting—has tremendous potential in transforming the therapeutic landscape for GCA.[91] These technologies, designed for targeted distribution, controlled release and regenerating abilities, have the potential to deliver more efficient, personalised and effective therapies for this recalcitrant disease.

The immunological safety of smart biomaterials and bioprinted constructs should also be carefully evaluated. Responsive polymers can release a product of their degradation activating local immune responses, whereas implanted constructs can induce a systemic inflammation if not adequately optimised. On the contrary, patient-specific 3D-printed scaffolds with naturally derived polymers or immunomodulatory factors can induce tolerogenic responses and vascular homeostasis.[92] For this reason, next-generation smart biomaterial design should aim at balancing effector function with immunological safety in order for it to retain translational potential in GCA.

Clinical application and efficacy

The biomaterials' clinical applications in the treatment of GCA are directed towards inflammation of the vascular system, which can lead to rupture of the arteries and vision loss effects. New and upcoming biomaterial technologies have been introduced to address therapy, which increases the delivery of drugs with fewer systemic side effects to achieve local treatment to inflamed blood arteries. Some of the biomaterials such as nanoparticles, hydrogels and degradable scaffolds have been proven to be potential in therapeutic applications by releasing drugs with anti-inflammatory effects over time and promoting vascular reconstruction. Some of these are used in several clinical applications, ranging from preclinical stages to clinical trial stages, to assess their efficacy and safety. Biomaterials' clinical application also strives to improve the quality of life in GCA patients by offering more personalised and effective treatments. Nanoparticle-based drug delivery systems, for example, can deliver drugs to inflammatory sites more specifically, minimising the impact on normal cells and increasing the therapeutic responses. Hydrogel-based therapy is also offering sustained drug release, maximising the compliance of treatment and minimising the frequency of delivery.

In vitro and *in vivo* studies have played an important role in determining the efficacy of biomaterials in treating GCA. These scientists perform *in vitro* models, like cultured endothelial cells and smooth muscle cells, in tests simulating GCA. These will allow us to assay the biocompatibility, anti-inflammatory activity and drug release kinetics of these materials. *In vivo* studies, like models of GCA in animals, have substantiated the capability of biomaterials to modulate inflammatory processes and promote vascular reconstruction.[2] Particulate systems incorporating anti-inflammatory drugs proved to be more efficacious in inhibiting arterial inflammation, whereas biodegradable scaffolds enable tissue regeneration. Preclinical models therefore provide significant information on the possible therapeutic benefits and drawbacks of biomaterial-based GCA therapy to be used as a reference for future clinical trials and applications.

Future perspectives

Biomaterial-based therapies will be the hallmark of the future of GCA therapy with objectives directed at maximising intervention specificity, efficacy and safety. As more is known about the pathophysiology for immune-mediated events and vascular inflammation of GCA, new biomaterials acting on these pathways will be created. This promising field of research is placed against the backdrop of nanotechnology, which is thought to provide the ability to target inflammatory tissues with specificity. Nanoparticles with anti-inflammatory drugs or bioactive molecules could be released locally at the site of inflammation, avoiding systemic side effects and delivering improved outcomes. These particles could also be designed to respond to environmental cues particularly, which will make therapeutic medicine act only in the presence of GCA-related inflammatory markers. Smart biomaterials will likely be the cornerstone of future GCA therapy. With

the capacity to respond to environmental stimuli dynamically like pH, temperature, or presence of certain enzymes, it may be possible to create high-precision drug delivery systems that not only deliver medicine but also control and modulate inflammation. The integration of biomaterials with cutting-edge technology such as 3D bioprinting promises much for vascular regeneration of GCA. The capability to print personalised scaffolds that mimic natural vascular structure and respond to inflammation has the potential to greatly improve the healing and tissue regeneration. In fact, bioprinting could also be capable of making easier generation of *in vitro* models for drug testing and potential for improved predictions of clinical efficacy. The integration of GCA therapy of the future, however, will depend on the integration of advanced biomaterial technologies to provide more targeted, sustainable and patient-specific therapy, ultimately maximising patient outcomes and quality of life.

Conclusion

GCA is an immune-inflammatory disease with vascular injury that is still difficult to treat effectively. Biomaterial advances such as nanoparticles, hydrogels and biodegradable scaffolds offer new promise for the treatment of GCA. Biomaterials are privileged with tailored drug delivery, controlled release and tissue regeneration. Therapeutic delivery is governed by local delivery of anti-inflammatory drugs, precluding systemic effects. Biodegradable scaffolds facilitate vascular regeneration and tissue integration with few side reactions; hydrogel-based systems can improve patient compliance with controlled drug release. Nanotechnology, smart biomaterials and 3D bioprinting are among the new technologies that are transforming biomaterial design. Nanoparticles are engaged in maximum specificity with minimum off-target effects, while smart biomaterials respond to environmental cues to deliver drugs in real-time. Meanwhile, 3D bioprinting can potentially print tailored scaffolds with the same native vascular geometry, thereby ensuring improved vascular regeneration. Further *in vitro* and *in vivo* studies are required to ascertain the safety, efficacy and long-term outcomes of biomaterial-based therapies. Clinical trials are required to validate therapy efficacy and translate into widespread clinical practice. The future of GCA treatment looks promising, thanks to the combination of biomaterials, precision medicine and innovative therapeutic techniques. These breakthroughs have the potential to substantially alter GCA care and provide a significant ray of hope for better outcomes and quality of life for such severely ill patients.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

Acknowledgement

Authors are thankful to their respective institutes.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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