REVIEW

Research on Liver Damage Caused by the Treatment of Rheumatoid Arthritis with Novel Biological Agents or Targeted Agents

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Abstract: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by polyarticular, symmetric, and aggressive inflammation of the small joints in the hands and feet, resulting in dysfunction. With progress and development in medicine, treatment of RA is constantly evolving, making several drugs available for the treatment of RA. From the nonsteroidal anti-inflammatory drugs (NSAIDs) at the start of illness to glucocorticoids and then to conventional synthetic DMARDs (csDMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs), therapeutic-use drugs for RA have been keeping pace with scientific research. However, various types of drugs have additional side effects when used over the long-term. New and emerging biological and targeted agents have been widely applied in recent years; however, the side effects have not been thoroughly investigated. In this paper, we review the research progress on liver damage caused by novel biological and targeted agents available for RA treatment. The aim is to provide a reference for rational clinical administration of such drugs.

Keywords: liver damage, novel biological agents, research progress, rheumatoid arthritis, targeted agents

Introduction

The etiology and pathogenesis of rheumatoid arthritis (RA) are unknown, but environmental factors, gene factors as well as environmental-genetic interaction are considered as major etiology of RA.Environmental factors especially cigarette smoking increase the risk of developing RA in those who have a hereditary disposition.[1] And the prevailing pathogenic model of RA assumes an autoimmune mechanism.[2] And the disease causes cartilage and bone destruction, resulting in degradation of joint functions, and even joint deformity and disability, seriously impairing the quality of life of patients.[3]

In recent years, novel biological and targeted agents have been increasingly used in the clinical treatment of RA, and compared to traditional anti-rheumatic drugs, significantly improve the clinical symptoms and slow down disease progression in patients. In the 2021 American College of Rheumatology (ACR) guidelines for the Treatment of Rheumatoid Arthritis, an adjustment was made with respect to bDMARDs and tsDMARDs as second-line therapy, especially tsDMARDs, which have a significantly improved therapeutic status compared to the previous guidelines, and reflected their efficacy and safety.[4] Currently, there are a relatively large number of novel biological agents clinically used for RA, including tumor necrosis factor inhibitors (TNFi), interleukin (IL) receptor antagonists, B-cell depleting agents, T-cell targeting drugs, etc. Targeted DMARDs mainly include Janus kinase (JAKs) inhibitors. They belong to different drug categories and have different pathophysiological targets and mechanisms of action (refer to Figure 1 and Table 1).

RA rarely affects the liver by itself but liver damage has been a common adverse effect in RA patients over long-term or on irregular medication intake. Liver damage occurs in RA patients, mostly during NSAIDs and methotrexate (MTX) therapy.[5]
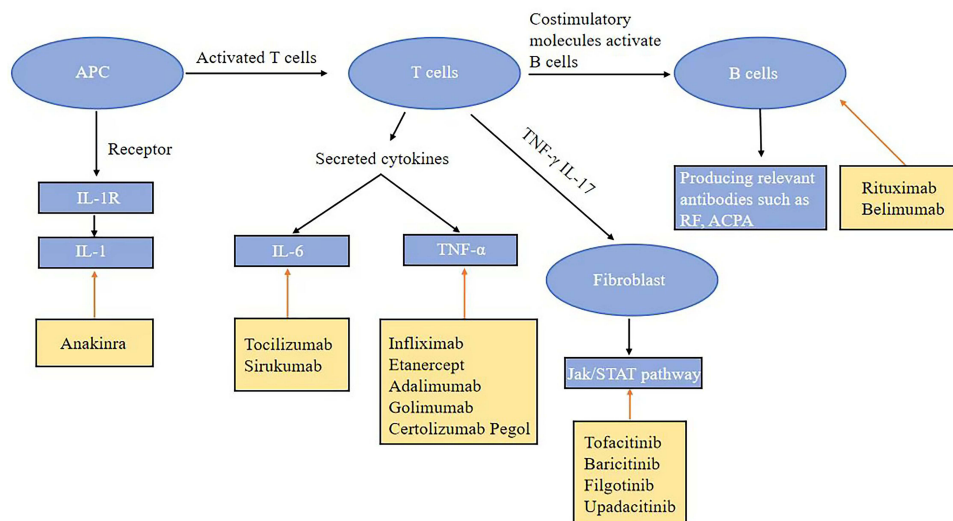
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Figure 1 Biological and targeted agents in the treatment of rheumatoid arthritis. Antigen-presenting cells deliver their own antigens via major histocompatibility complexes to T cells, releasing lymphokines and activating macrophages to provide assistance to B cells. The latter may be induced to produce autoantibodies such as anti-citrullinated proteins. Autoantibodies are bound to the respective autoantigens and form immune complexes in the synovial membrane. These immune complexes bind to macrophages and other cells via Fc receptors and complement receptors, activating the secretion of pro-inflammatory cytokines and other inflammatory mediators like tumor necrosis factor, interleukins and macrophages via lymphokines, such as T-cell interferon or IL-17.

Methotrexate used for RA has been generally well tolerated, however, it has potential side effects like hepatotoxicity and cytopenia.[6] In the application of leflunomide for RA, the elevation of liver enzymes usually occurs in the first six months of treatment and remains unresolved until follow-up.[7] Leflunomide has been reported to increase the incidence of abnormal liver enzymes by 14%–22%.[8] Hydroxychloroquine sulfate also bears certain side effects in the treatment of RA, including abnormal elevation of transaminases.[9] Comparatively, liver damage is relatively uncommon with novel biological and targeted agents and may range from a slight increase in transaminases to severe forms of hepatotoxicity. In this paper, we summarize the mechanisms of action and possible manifestations of liver damage caused by novel biological and targeted agents in the treatment of RA in recent years, to provide guidance for clinical use.

Table 1 Currently Approved Biological DMARDs and Targeted Agents

Target	English Generic Name	Type	Approved on USA
TNF-α	Infliximab	Human-mouse chimeric IgG1 antibody	1999
	Etanercept	TNF-α receptor IgG1 Fc fusion protein	1998
	Adalimumab	Fully human IgG1 antibody	2003
	Golimumab	Humanized IgG1 antibody	2009
	Certolizumab Pegol	PEG modified anti-TNF-α antibody Fab fragment	2009
IL-1	Anakinra	IL-1 receptor antagonist	2003
IL-6	Tocilizumab	Humanized IgG1 antibody	2010
	Sirukumab	Fully human antibody	2017
CD20	Rituximab	Human-mouse chimeric IgG1 antibody	2006
BLyS	Belimumab	Fully human IgG1 antibody	2011
CTLA-4	Abatacept	CTLA-4 antigen extracellular region-Fc fusion protein	2006
JAK1, JAK2, JAK3	Tofacitinib	Intracellular enzyme	2012
JAK1, JAK2	Baricitinib	Intracellular enzyme	2018
JAK1	Filgotinib	Intracellular enzyme	–
JAK1	Upadacitinib	Intracellular enzyme	2019

Note: Approval date refers to the time when the RA indication is approved.

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TNF-α Inhibitor

Tumor necrosis factor alpha (TNF-α) plays an important role in the development of inflammation. Elevated levels of TNF-α have been observed in the synovium of RA patients, which is closely associated with the development of bone erosion.[10] TNF-a inhibitors primarily include infliximab, etanercept, adalimumab, golimumab, and certolizumab. TNF-a inhibitors are potent therapeutic agents for RA, and can greatly alleviate the inflammatory state, while revolutionizing the management of RA by blocking cytokines characteristic of the innate immune system. Abnormalities in liver function tests may occur during anti-TNF-α therapy, including transient and self-limiting high aminotransferases, cholestatic disease, and hepatitis, which, in some cases may be severe or life-threatening.[11]

Infliximab

Infliximab (INF) is a monoclonal antibody targeting TNF-α that has been demonstrated to be effective in patients with RA. As observed by a multicenter study involving 6861 patients with RA, INF has the highest correlation with elevated liver function tests (LFTs) within the range of TNF-α inhibitors to the abnormal range.[12] A randomized 1-year trial demonstrated a balanced incidence of adverse events regarding liver injury between the two groups using salazosulfa-pyridine and hydroxychloroquine or infliximab.[13] It seems that infliximab-induced hepatitis is maintained by immune-mediated mechanisms simulating the features of type I autoimmune hepatitis[14] with elevated antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), and anti-double-stranded DNA antibodies (anti-dsDNA). However, the exact pathogenesis of its induced autoimmune hepatitis is unknown. Available evidence suggests that the incidence of liver injury in RA patients on infliximab is significant but relatively rare, and often resolves spontaneously with a favorable prognosis after discontinuation of the drug.

Etanercept

Etanercept (ETN) is the first specific anti-cytokine drug approved for the treatment of RA. Adverse effects are rare in terms of elevated liver enzymes and autoimmune hepatitis.[15] In terms of liver damage, ie, cirrhosis, a multicenter study revealed no correlation with the development of cirrhosis in RA patients.[16] In terms of hepatitis virus infection, Brunasso et al published a systematic review[17] which included 153 patients with HCV treated with anti-TNF-α drugs between 1999 and 2010, including 91 with RA, 7 with psoriatic arthritis, 8 with psoriasis, 8 with both psoriasis and psoriatic arthritis, 6 with CD, and 14 with other chronic inflammatory diseases. A total of 110 cases were treated with ETN, with only one clearly diagnosed case of worsening HCV hepatitis and five suspected cases. The liver showed improvement after discontinuation of ETN, indicating that it appears to have a favorable safety profile in terms of hepatitis virus infection.

Adalimumab

Adalimumab (ADA) is a human IgG1 monoclonal antibody binding soluble transmembrane TNF-α, which can block the interaction of cell surface TNF receptors, to achieve immunosuppressive effects.[18] Multiple randomized controlled trials have demonstrated significant efficacy of ADA in patients with early and long-term RA.[19,20] In studies assessing ADA for RA, asymptomatic alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations have been reported, however, the phenomenon is reversible with the discontinuation of ADA.[21] In a 7-year clinical study, the association between ADA and elevated AST/ALT was identified to be modest compared to the control group on DMARDs.[12] Furthermore, evidence suggests that there may be potential benefits of ADA in the treatment of specific liver diseases.[22] In patients with concomitant HCV and HBV infection, data suggests that ADA does not alter viral load or liver enzyme levels or activate HBV and/or HCV. There is also a slight reduction in liver fibrosis scores before and after treatment, reflecting that the use of ADA in patients with combined HBV or HCV infection appears to have a favorable safety profile.[23]

Golimumab

Golimumab (GOL) is one of the TNF-α inhibitors approved for the treatment of RA. It is a human IgG1κ monoclonal antibody produced from a mouse hybridoma cell line with recombinant DNA technology. It mainly acts by targeting and

neutralizing TNF-α to prevent inflammation, and cartilage and bone destruction. Compared to other anti-TNF drugs, GOL features a lower discontinuation rate and better tolerability.[24] During a follow-up observation of 5154 Japanese RA patients treated with GOL, acceptable safety and efficacy were observed in all patients, and concomitant use of MTX was associated with increased efficacy, while persistence was associated with GOL.[25] However, as a potent inhibitor of TNF-α, GOL may result in the relapse of chronic hepatitis B in susceptible patients.[26]

Certolizumab Pegol

Certolizumab Pegol (CZP) is a TNF-α inhibitor that can selectively neutralize the inflammation site by covalently binding polyethylene glycol (PEG) to the Fab fragment of recombinant human anti-TNF-α antibody, thereby binding with high affinity to human TNF-α. Nanau et al identified a low incidence of severe AEs in patients with CZP, with major AEs occurring in the neurological and respiratory systems.[27] Currently, there is no evidence of adverse hepatic effects associated with pexelizumab treatment for RA.

To conclude, the administration of TNF-α receptor blockers in the autoimmune setting may result in liver injury, especially in the presence of pre-existing autoimmune serological signs. The incidence of liver injury resulting from anti-TNF-α therapy, though relatively low, is still significant. For patients with significantly elevated transaminases or clinical symptoms consistent with acute hepatitis, anti-TNF-α therapy should be discontinued prior to the onset of severe irreversible damage. The safety of anti-TNF-α drugs in the context of HCV infection appears to be acceptable, however, long-term and large controlled clinical trials are required for validation.

Interleukin Receptor Antagonists

Interleukin (IL) is an important pro-inflammatory cytokine in the pathogenesis of RA, and IL-1 and IL-6 are key cytokines in driving the inflammatory and destructive process in RA. They have an important role in the pathogenesis of RA.[28] The inflammatory response in the synovium results in the production of cytokines such as IL-1 and IL-6, thereby activating osteoclasts and mediating articular cartilage and bone destruction.[29] IL-17 is predominantly highly expressed in the synovial fluid of RA patients and is mainly associated with bone degradation.[30] Presently, interleukin receptor antagonists are available for the treatment of rheumatoid arthritis, ankylosing spondylitis, arthritic psoriasis, etc.

IL-1 Receptor Antagonists

IL-1 is an important cytokine in the pathogenesis of RA. Natural IL-1 receptor antagonist (IL-1RN) is an anti-inflammatory protein and its combination with IL-1RN plays an important role in maintaining the immune homeostasis of the body.[28] The expression of natural IL-1 receptor antagonists in the synovial tissue is reduced in patients with RA.[31]

Anakinra, a recombinant IL-1 receptor antagonist with anti-inflammatory and immunomodulatory effects, is the only IL-1 receptor antagonist currently used in RA. Studies have demonstrated that anabolic acid is a safe, effective, and a well-tolerated biological agent.[32] Currently, no clear supporting data is available on liver damage due to anabolic agents for RA, Several randomized controlled and cohort trials have not demonstrated statistically significant differences in adverse events between anabolic agents and placebo in the treatment of RA.[33,34]

IL-6 Receptor Antagonists

Interleukin-6 is an important cytokine with pleiotropic and redundant functional activity. In RA, IL-6 plays an important role in the inflammatory processes, osteoclast-mediated bone resorption, and the development of vascular opacification, contributing to the development of IgM and IgG rheumatoid factors and antibodies to guanosine peptides, thus contributing to the characteristic increase in guanosine peptides.[35] Some studies have identified that serum IL-6 levels were higher than normal in RA patients and that after treatment with DMARDs, serum IL-6 levels were significantly reduced, relieving the disease symptoms.[36] Currently, IL-6 receptor antagonists like tocilizumab and sirukumab have been marketed and are in Phase 3 clinical trials.

Tocilizumab

Tocilizumab (TCZ) is a recombinant humanized anti-IL-6 receptor (IL-6R) monoclonal antibody inhibiting its binding to its receptor and reducing the pro-inflammatory activity of this cytokine, by competing with the soluble and membrane-bound forms of human IL-6 receptor 17.[37] A 72-week randomized double-blind controlled trial identified that TCZ infusion add-on therapy has been highly effective and well tolerated in South Korean patients with active refractory RA compared to conventional DMARDs, with significant remission of DAS28. However, patients in the TCZ group had significantly more-frequent liver function abnormalities, mainly in the form of elevated mean AST and ALT levels, compared to the placebo group, but most of the liver function abnormalities were mild or moderate in intensity and asymptomatic in presentation.[38] Amouzougan et al also demonstrated that TCZ alleviated RA symptoms, with liver enzyme levels one to two times the upper limit of normal without exhibiting any adverse effects, indicating that TCZ allows for adequate liver function and clinical safety.[39]

Sirukumab

Sirukumab (SRK) is an IgG1κ human anti-IL-6 monoclonal antibody binding to IL-6 to prevent IL-6-mediated down-stream effects. SRK is an effective and well-tolerated tool for novel treatment of patients with active RA, and experts have recommended that SRK at 50 mg/4 weeks or 100 mg/2 weeks be used for the treatment of population with RA.[40] The profile of adverse events appears to be like that of TCZ, most commonly with elevated liver enzymes, however, dose response to SRK has not been demonstrated. In a randomized controlled study, a mild increase in transaminases has been observed in patients with RA treated with SRK initially. It gradually resolved after 4 weeks of treatment, reflecting the relatively favorable safety profile.[41] Results from another phase 3 clinical trial with Sirukumab in Japanese patients with refractory rheumatoid arthritis and poor results who were treated with TNFi, demonstrated that only a small number of patients treated with Sirukumab had ALT and AST levels above the normal range. This suggests that adverse effects in patients needed to be observed closely when administering the drug clinically.[42]

At the initial stage of administration, interleukin factor antagonists may result in elevated transaminases, in particular tocilizumab, which may be associated with disruption of fat metabolism and NAFLD. Therefore, it is necessary to monitor transaminases during the first 6 months of treatment.

B-Cell-Depleting Agents

B cells have an important role in the development of RA, and the mechanisms of action mainly include the production of antibodies, such as rheumatoid factor, the production of inflammatory cytokines, such as IL-6 and IL-17, and the activation of T cells in the pathogenesis of RA.[43] Currently, the main B-cell-depleting agents already available for clinical treatment of RA include rituximab and belimumab.

Rituximab

Rituximab (RTX) is a monoclonal antibody targeting the CD20 molecule on B lymphocytes and serves as the standard of care for RA. A randomized, double-blind, multicenter trial involving 517 patients with RA demonstrated that some patients rapidly developed acute liver failure and jaundice, often referred to as acute hepatic necrosis, after initiation of rituximab, which may be associated with toxicity or ischemic injury.[44] Nevertheless, a retrospective clinical study with a duration of 9.5 years demonstrated no significant difference in the incidence of adverse events between rituximab and placebo.[45]

Belimumab

Belimumab is a fully human IgG1 monoclonal antibody targeting B-cell activation factors, thereby inhibiting B-cell activation. Belimumab has been proven to be a safe and effective drug in the treatment of SLE and of developmental value in the treatment of RA.[46] Currently, no clear supporting data on liver damage due to belimumab for RA is available, and some randomized controlled trials have demonstrated no statistically significant differences in adverse events between belimumab and placebo in the treatment of RA.[47]

The risks of liver damage resulting from B-cell-depleting agents are relatively low, and rituximab is a relatively safe option for patients with RA not combined with viral hepatitis. However, compared to TNF-α inhibitors, B-cell-depleting agents are relatively infrequently used in the clinical treatment of RA, and further clinical trials are still required to provide more data on the association with liver damage.

T-Cell-Targeted Drugs

T cells modulate the course of disease in RA at multiple levels and are a logical option for anti-inflammatory therapy. Therapeutic interventions against T cells may target antigen recognition or interfere with co-stimulatory processes. The most widely recognized co-stimulatory routes involve CD28, cytotoxic T lymphocyte-associated protein 4 (CTLA-4), CD80, and CD86. The major T-cell-targeting drug currently available for clinical application in RA is abatacept.

Abatacept is a designed protein and blocks the connection of CD28 to CD80 and CD86, thereby preventing the activation and proliferation of CD4+ T cells. Reynolds and Zen et al identified the possibility of hepatitis in patients receiving CTLA-4 inhibitors.[48,49] A study conducted between January 1, 2006, and June 30, 2021 collected a total of 77,669 adverse events with abatacept and 2889 reports of hepatitis B virus reactivation (HBVr) with other drugs,[50] based on the use of the FDA Adverse Event Reporting System (FAERS) database. All 55 cases taking abatacept reported serious adverse events, including 6 hospitalizations and 4 deaths.

JAK Inhibitor

Janus kinases (JAKs) are non-receptor tyrosine kinases in the cells and play a key role in the signaling pathway of cytokines. The dysregulation of the signal transducer and activator of transcription (STAT) pathway of JAKs has been associated with various immune disorders. In recent years, the choice of drugs targeting components of the JAK-STAT pathway has been widely noticed as a potential new treatment for RA, demonstrating promising efficacy in improving the clinical symptoms of RA. Currently, four oral JAK inhibitors have been approved for the treatment of RA, including tofacitinib, baricitinib, upadacitinib, and filgotinib.

Tofacitinib

Tofacitinib (TOF) is a small synthetic molecule targeting JAK1 and JAK3 as an inhibitor. Studies have demonstrated that TOF may significantly inhibit IL-17 and IFNc production by synovial and peripheral blood CD4+T cells, reduce IL-6 production in synovial fibroblasts, and further inhibit the progression of structural damage in arthritic joints, while improving health-related quality of life (HR-QOL) by reducing RANKL production.[51] Tofacitinib is typically well tolerated, with most adverse events being mild or moderately severe. Elevated serum creatinine level is the most common adverse effect of TOF.[52] A prospective study revealed elevated ALT or AST in patients exposed to TOF compared to placebo,[53] however, only two studies in a review describing efficiency, retention, and safety have reported elevated liver enzymes. The current evidence indicates that oral TOF is an effective and safer option in the treatment of patients with RA, although large long-term follow-up studies are required for further confirmation.

Baricitinib

Baricitinib is an orally available reversible inhibitor of Janus kinases JAK1 and JAK2, often administered in patients with moderately or severely active RA. Findings from a 52-week phase 3 clinical trial have demonstrated a significant inhibition of radiographic progression of joint injury and a higher ACR20 response rate in patients in the baricitinib group compared to the placebo and adalimumab groups. Clinical symptoms significantly improved in patients,[54] but were accompanied by a higher incidence of adverse events in the baricitinib group. Baricitinib has been reported to be associated with elevated liver enzyme levels, and in the control study, elevated ALT and AST have been observed in patients treated with baricitinib at week 16, with most cases of elevated liver transaminases being asymptomatic and transient.[55] The RA-BEGIN study concluded that baricitinib requires no dose adjustments in patients with mild or moderate hepatic impairment, however, baricitinib is not recommended in patients with severe hepatic impairment.[56]

Filgotinib

In clinical drug trials of upadacitinib and filgotinib, transient elevations in Grade 1 or 2 AST and ALT levels have been reported without any drug-induced hepatocellular injury, and the incidences of Grade 3 or 4 AST/ALT elevations have been lower than that of MTX.[57] In a long-term, open-label extension study, the safety and efficacy of filgotinib, with or without MTX, has been evaluated in patients with RA. Excellent tolerability and safety were demonstrated for filgotinib + MTX and filgotinib monotherapy groups.[58]

Upadacitinib

Studies have demonstrated that the manifestations of liver damage in RA patients treated with upadacitinib are mainly elevated ALT or AST levels that are not severe.[59] In a 24-week, phase 3, double-blind, controlled trial,[60] patients were randomly assigned to receive oral upadacitinib or intravenous abciximab in a ratio of 1:1. Each drug was administered in conjunction with a stable synthetic DMARD—liver transaminase levels were higher in the upadacitinib group than in the abatacept group. Around 2.6% of patients treated with upadacitinib experienced Grade 3 ALT and AST level elevations and 0.3% reported Grade 4 elevations, however, none of the patients met Hay's Law criteria suggestive of drug-related liver injury. In a UPA pharmacokinetic study of 18 patients with cirrhosis, using Child-Pugh Class A and Class B, as well as matched healthy controls, the baseline AST, ALT, and bilirubin had no effect on upadacitinib exposure over a very short period.[61]

Currently, JAK inhibitors are novel targeted drugs for RA treatment. Recent studies have demonstrated that four JAK inhibitors have better safety profiles but are limited by the short duration of clinical application. More recent study data is required to further illustrate the safety of JAK inhibitors.

Others

There are also some biosimilars among the latest drugs available for the treatment of RA. Infliximab biosimilars CT-P13 and SB2 were approved in 2016 and 2017, respectively, and both have similar therapeutic efficacy and safety profiles compared to infliximab and induced comparable liver injury compared to infliximab.[62] Other biologics such as levilimab (targeting interleukins or the receptors), satralizumab and cytokine or chemokine-targeted biologics such as mavrilimu-mab and otilimab are still used in clinical trials. Although different biosimilars have demonstrated efficacy and safety compared to the reference product, serious adverse reactions may not have been fully identified and confidence in their use is still lacking.

Conclusion

TNF-α inhibitors are first-line biologics for the treatment of RA and the first biologics used in RA. The incidence of liver damage may be low, however, acute liver injury and significant increases in transaminases are required. It should be noted that Chinese patients with RA using TNF-α inhibitors should be highly alert to the risk of hepatitis B virus replication and tuberculosis relapse. Interleukin factor antagonists may result in elevated transaminases during the initial administration, and monitoring of liver function is essential during dosing. B-cell-depleting agents are frequently administered as second-line agents in RA, mostly in patients who fail to respond to treatment with TNF-α inhibitors or interleukin antagonists. Attention should be paid to whether the patient has viral hepatitis when administering B-cell antagonists; rituximab may result in viral reactivation. The safety of B-cell antagonists is more reliable in patients who do not have viral hepatitis. T-cell-targeted drugs are second-line biological agents for RA, which have a relatively high potential to cause adverse events such as liver damage. Regular monitoring of liver function is recommended during drug administration, and it is not indicated for patients with abnormal liver function or viral hepatitis. The incidence of tumors and infections resulting from JAK inhibitors is comparable to that of TNF-α inhibitors, and both hepatitis B and tuberculosis screening should be completed prior to treatment.

The effects of biologics on the liver represents a particularly important part along with the therapeutic effects. The long-term effects of TNF-α inhibitors and JAK inhibitors on the liver are expected to be of major focus in future research. The increasing incidence of liver disease emphasizes the necessity to be more cautious when prescribing anti-rheumatic

drugs due to their hepatotoxicity. According to study data, all drugs may result in elevated liver enzymes early in their administration, and the monitoring of changes in transaminase levels is critical for all patients with RA, especially those treated with combined methotrexate and leflunomide. Furthermore, prior to initiating treatment with bDMARDs, RA patients should be screened for chronic HCV and closely monitored for liver enzymes as well as HCV viral load. In patients with chronic HCV, ACR recommends that etanercept be administered, while in patients with acute or chronic HCV with severe liver damage (Child-Pugh classification B or C), biological agents should be avoided. In patients with RA who are infected with HBV, concomitant anti-hepatitis B virus medication should be administered, while liver function and nucleic acid levels should be monitored for viral replication.

The clinical application of new biological and targeted agents provides new approaches and ideas for the treatment of RA. With the publication of further data on clinical efficacy and safety, an increasing number of biological and targeted agents with different targets of action will be approved for the clinical treatment of RA, and may play an important role in alleviating the clinical symptoms in RA patients, thus preventing inflammation from worsening and ultimately improving patients' quality of life.

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Disclosure

The authors report no conflicts of interest in this work.

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