Combining Therapeutic Drug Monitoring with Biosimilars, a Strategy to Improve the Efficacy of Biologicals for Treating Inflammatory Bowel Diseases at an Affordable Cost

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Key Words

Biologicals · Therapeutic drug monitoring · Pharmacokinetics · Anti-drug antibodies · Biosimilar

Abstract

Background: Biologicals provide a tight disease control but not all patients respond favourably to treatment. Some patients do not respond at all (primary non-responders), while other patients respond initially but show loss of response over time (secondary non-responders). Drug concentrations in the serum of patients can be monitored and correlated with biological, clinical or endoscopic response. Therapeutic thresholds have been defined for infliximab and adalimumab. The European Medicines Agency has approved 3 biosimilars of infliximab and new biosimilars are waiting approval.

Key Messages: Distinguishing primary non-responders from patients with insufficient drug exposure during induction through drug serum concentration determination will improve drug efficacy. Current algorithms to guide treatment of patients with secondary loss of response take into account that patients with high titers of anti-drug antibodies (ADA) do not respond to dose intensification and that patients with

therapeutic drug concentrations cannot be switched to biologicals within class. For patients in clinical remission, the cost of biological treatment can be decreased by dose tapering patients with supra-therapeutic concentrations and/or by switching patients with adequate drug concentrations and no formation of ADA to biosimilar, whereas efficacy can be increased by dose-intensifying patients with low or transient ADA and by switching patients with persistent ADA to biologicals within or out-of class. **Conclusions:** As an objective tool, therapeutic drug monitoring can identify patients who are eligible for dose tapering, intensification of treatment, cessation of treatment, switching within- or out-of class and switching to biosimilar.

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Published by S. Karger AG, Basel

Introduction

Inflammatory bowel diseases (IBD) encompass 2 well-established but not entirely discrete disease entities, Crohn's disease (CD) and ulcerative colitis (UC). Over 1 million residents in the United States and 2.5 million in Europe are estimated to have IBD [1]. Chronic inflam-

matory diseases typically start early in life, thereby strongly affecting the quality of life and productivity of young and active individuals. Work productivity is often decreased, especially when the disease is poorly controlled. Since there is no cure available, patients have to be treated lifelong. This requires safe, tolerable and cost-effective treatments. In the past 20 years, the medical management of IBD has changed considerably. In 1999, the European Medicines Agency (EMA) authorized the marketing of Remicade® (INN-infliximab, IFX), the first available biological to target the proinflammatory cytokine tumour necrosis factor (TNF)- α . Subsequently, 2 other anti-TNF biologicals, Humira® (INN-adalimumab, ADM) and Simponi® (INN-golimumab, GOL) have been approved for treatment of UC/CD and UC, respectively. Recently, Entyvio® (INN-vedolizumab, VEDO), obtained marketing approval in Europe for treatment of UC and CD. Vedolizumab is a monoclonal antibody blocking the interaction between $\alpha_4\beta_7$ integrin on lymphocytes and the mucosal addressin cell-adhesion molecule protein-1 on endothelial cells, thereby hampering lymphocyte migration to inflamed areas of the gut [2]. Biologicals usually provide a tight disease control and use of these powerful drugs leads to a better quality of life, decreased disability and improved work/school productivity. However, not all patients will respond favourably to treatment with biologicals. Some patients do not respond at all (primary non-responders), while other patients respond initially but show loss of response over time despite increased doses and/or more frequent administration of the drugs (secondary non-responders). One of the main causes for this loss of response is the formation of anti-drug antibodies (ADA), which lower the serum levels of biological drugs by inactivating the drug and by increasing the clearance, leading to the premature termination of therapy [3]. Drug concentrations in serum of patients can be monitored and correlated with biological, clinical or endoscopic response. A drug concentration–response has been demonstrated for infliximab, adalimumab and golimumab and optimal infliximab and adalimumab concentration thresholds have been defined for different outcomes such as clinical response, clinical remission, mucosal healing, decrease in C-reactive protein, ... [4–11]. The pharmacokinetics and pharmacodynamics of biologicals are potentially influenced by many factors, such as gender, weight, age, disease type and severity, ADA, albumin, co-medication and other unidentified factors [12, 13]. Pharmacokinetics is inferred from an analysis of a population of patients. A population model identifies the pharmacokinetic model that best describes

‘the typical patient’, identifies those covariates that are important for this drug in this cohort of patients and quantitates the variability in the kinetics of the drug between individuals [14]. Subsequently, the dosage regime can be adjusted to reach a target in a particular patient for a particular drug at a particular ‘disease moment’ and this dosage regimen is determined by drug characteristics, patient (baseline) characteristics and the formation of ADA. Therapeutic drug monitoring (TDM) is a tool which, on the basis of the drug and anti-drug antibody concentrations measured in serum, allows the dose of biological to be adjusted in order to maintain or regain response [15]. Quantifying the immune response through the measurement of ADA provides valuable information on whether undetectable or low drug concentration is caused by the neutralization of the drug. However, most of the ADA assays are drug sensitive and this hampers the detection of ADA in the presence of the drug. Recently, a number of drug-tolerant anti-drug antibody assays have been described that can detect antibodies in the presence of the drug [16–18]. In addition, TDM could also be used to dose reduce patients with supra-therapeutic concentrations [4].

Decreasing Proportion of Primary Non-Responders

Primary non-response is defined as lack of improvement of clinical signs and symptoms after the induction phase leading to the discontinuation of the drug [19]. In a real-life cohort study, primary non-response is often defined as no benefit after a median of 2 administrations and discontinuation of treatment [20]. For the anti-TNF biologicals, primary non-response has been attributed to ‘non-TNF-driven disease’, which is a simplified approach of the problem. A recent paper suggested that patients who respond but fail to achieve remission, which is a combination of both patients who partially respond but do not remit and patients who have no response at all, are likely almost all due to insufficient drug [21]. The clinical evaluation of the patient after the induction phase should therefore take into account drug serum concentration and if drug concentration is below the threshold value, drug intensification should be considered, whereas patients with a lack of response and concentrations above threshold can be considered to be true non-responders and could be switched to a biological out of class. Distinguishing primary non-responders from patients with insufficient drug exposure during induction will improve drug efficacy (fig. 1).

Fig. 1. Future treatment strategy for patients starting biological treatment. Based on patient factors influencing pharmacokinetics, patients can be subdivided into patients requiring low, standard or high-induction doses. From start of therapy, drug and anti-drug concentrations need to be monitored in this treat to target strategy. Upon adequate clinical response, patients can continue maintenance treatment. Upon inadequate clinical response, drug serum concentration can guide clinicians to intensify treatment or to switch to another biological.

Guidelines on Secondary Non-Responders

When patients show loss of response to biologicals, treatment is adjusted by using one out of 3 empirical strategies: (1) intensifying therapy by creasing the dose or shortening the dose-interval of the biological; (2) switching to a biological with the same target (within class: for example from infliximab to adalimumab); (3) switching to a biological with a different mechanism of action (out of class: for example from infliximab to vedolizumab) [12]. This strategy, however, is often inadequate, since patients with high titers of ADA will most likely not respond to dose intensification, and patients with loss of response who have therapeutic drug concentrations are unlikely to respond to treatment with another biological with the same mechanism of action. Recently, a number of studies have included TDM as a guideline for treating algorithms for patients losing response to biologicals. These algorithms take into account that patients with high titers of ADA will most likely not respond to dose intensification and that patients with therapeutic drug concentrations are unlikely to respond to treatment with a biological with the same mechanism of action [22–24].

Optimizing Patients in Clinical Remission

The challenge of the future is to improve the efficacy of biologicals without increasing costs inherent to biologicals, since infliximab and adalimumab currently are responsible for incurring the heaviest medicinal expenditures in many countries [25]. This could be done by treatment optimization of patients in clinical remission that continue treatment, since it has been shown that half of these patients may still have an active inflammation as gauged by biochemical or endoscopic measures [26, 27].

Patients in clinical remission with drug concentration above the upper threshold value could be eligible for a dose decrease or an interval increase based on the condition that the drug is continuously monitored in order that patients do not get underexposed. The fact that patients in clinical remission with drug concentrations above the threshold value can be dose reduced without decreasing clinical outcome was effectively illustrated by the landmark TAXIT trial in which 263 patients receiving maintenance therapy for at least 14 weeks and in stable clinical response, defined as being symptom-free (full

responder) or having clear clinical improvement with obvious decrease of disease activity but with still clinical symptoms (partial responder) were included [4]. Upon inclusion, 44% of patients had infliximab trough concentrations within the defined threshold of 3–7 µg/ml. Of the remaining 148 patients, 51% underwent dose escalation and 49% underwent dose reduction in order to achieve trough concentration within the 3–7 µg/ml window and to be randomized into groups that received infliximab dosing based on their clinical features or continued dosing based on infliximab trough concentrations. In the dose-reduction group, no significant change was observed in the proportion of CD and UC patients in remission. Thus, the cost of biological treatment could be decreased by dose tapering patients in clinical remission with supra-therapeutic drug concentrations.

Patients in clinical remission with a trough concentration within the therapeutic range could be considered for switching to a biosimilar. In September 2013, EMA issued the marketing authorisation of the first biosimilar of Remicade®, CT-P13, to 2 applicants, Celltrion Inc. (Incheon, South Korea) and Hospira Inc. (Lake Forest, Ill., USA) under the trade names Remsima® and Inflectra® respectively. Both drug products are manufactured by Celltrion Inc. In 2016, the EMA committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on SB2, an infliximab biosimilar of Samsung Bioepis. The CHMP's positive opinion was referred to the European Commission, which formulated a positive advice on the grant of a marketing authorization for SB2. Recently granted, SB2 is commercialized under the trade name Flixabi® by Biogen in the European Union. In addition, biosimilars of adalimumab are making their way to the market. Because of their intrinsic complexity and being dependent on the manufacturer, a biosimilar cannot be seen as an exact copy of its originator product [28]. Approval of Remsima® and Inflectra® implies that all major physicochemical characteristics and biological activities of the biosimilar were shown to be comparable to those of Remicade®. Even though significant differences in the amount of fucosylation have been observed, the European regulatory authorities concluded that these differences do not have an impact on the clinical properties. Previous randomized controlled trials indeed demonstrated the bioequivalence and therapeutic equivalence for CT-P13 in ankylosing spondylitis and rheumatoid arthritis patients [29, 30]. These results were extrapolated to IBD for the purpose of approval by EMA. After approval, few studies reported efficacy data after induction therapy with CT-P13 in IBD patients [31–

33]. Still many clinicians doubt the effectiveness and safety of biosimilars because of the lack of experience with these products and the lack of knowledge about their immunogenic potential and do not prescribe biosimilars although 20–34% less expensive than the originator. If used, biosimilars are used to start therapy in naïve patients. The NOR-SWITCH trial (NTC02148640) is a randomized, double-blind, parallel-group study to evaluate the safety and efficacy of switching from innovator infliximab (Remicade®) to biosimilar infliximab (Remsima®) compared with continued treatment with innovator infliximab in patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, UC, CD and chronic plaque psoriasis. This study has included 500 patients, has a time frame of 52 weeks and primary outcome is worsening of the disease condition. Results are expected in January 2017. In the meantime, a prospective observational study investigated the efficacy, safety, pharmacokinetic profile and immunogenicity following a switch from Remicade® to CT-P13 in 83 IBD patients in the Netherlands. Switching from Remicade® to CT-P13 had no significant impact on short-term (16 weeks) clinical outcomes [34]. Pharmacokinetic parameters such as drug concentrations were maintained during the study. During the 16 weeks follow-up, 2 patients developed new detectable ADA and 5 patients discontinued CT-P13. A limitation of the study was the lack of a control group that allowed patients to continue Remicade®. Furthermore, 5 patients had detectable ADA before inclusion and had detectable ADA towards CT-P13 during the study. The cross-reactivity of ADA towards Remicade® versus the biosimilar was already shown by 2 other studies [35, 36]. The switch study did not mention if these were the 5 patients that needed to stop treatment. This study does provide solid evidence that switching from the originator to a biosimilar is safe and effective. Since ADA were measured using a drug-sensitive assay, it cannot be concluded that the newly detected ADA in the 2 patients that developed ADA during the 16 weeks were pre-existing. Therefore, switching during maintenance treatment can be performed in patients with adequate drug concentrations and no ADA measured using a drug-tolerant anti-drug antibody assay (fig. 2). Patients with therapeutic drug concentrations but measurable ADA should not be switched and drug and ADA should be monitored closely to determine if antibodies are transient or persistent [37]. In case of persistent antibodies, antibody titer will most likely increase with time leading to an excess of antibody over drug, an undetectable drug concentration and consequently loss of clinical response.

Fig. 2. Future treatment strategy for patients in clinical remission. Drug serum concentrations in patients in clinical remission receiving maintenance treatment should be measured at least every 24 weeks. If drug concentration is above threshold, dose can be decreased by increasing the interval or decreasing dose. To prevent patients from getting underexposed, drug concentrations should be monitored at every administration until stable drug concentrations are observed. Once the drug concentration is within the therapeutic range, an ADA assay that allows the detection of antibodies in the presence of the drug can be performed. In the absence of

ADA, patients can be switched to biosimilar. In the presence of ADA, drug and ADA should be monitored more frequently. Patients in clinical remission with undetectable drug concentrations and no ADA should be checked for compliance in case of self-administered drugs. Patients in clinical remission with low or no drug concentrations and low or no ADA should be dose intensified to avoid the formation of persistent ADA and carefully monitored. Patient with persistent ADA should stop treatment and the clinician and patient should together make a decision on the course of treatment to continue with.

Underexposure to the drug leads to secondary loss of response, which often evolves into disease progression and, in case of IBD, to surgical resections of the inflamed bowel. TAXIT revealed that in patients with sub-therapeutic concentrations dose escalation increased the number of CD patients in remission from 65% before optimization to 88% after dose escalation, whereas for UC patients dose escalation did not significantly affect the proportion of patients in remission [4]. Dose escalation is however not recommended when patients develop high titers of antibodies since increasing the dose will only lead to an increased antibody formation. Patients with high antibody titers should therefore be switched to another biological within- or out-of-class but not to a biosimilar. Since it has been shown that antibodies towards infliximab do not cross-react with adalimumab, patients developing high titers of antibodies towards infliximab can be switched to adalimumab but have a higher risk to develop

antibodies towards a second biological [38]. In addition, the formation of antibodies can sometimes be transient and overcome by increasing the dose, shortening the interval or by adding an immunomodulatory [18, 37, 39–41]. The question as to when patients have to stop treatment and switch to another biological arises. Recently, Roblin et al. [18] showed that stable ADA towards infliximab (ATI) defined by at least 2 consecutive time points were associated with loss or response, whereas transient ATI had no impact on loss of response rates. Detection of ADA is often a qualitative approach to define ADA positivity and so far, an optimal cut-off titer could not be defined due to 3 hurdles. The first hurdle was the variety of assays to determine ADA from homogenous mobility shift assays, over cell-based assays to radio immune assays and ELISA. The different formats detect different types of antibodies and have different sensitivities. The second hurdle was inherent to the assay and concerns the drug

tolerance. Many assays do not detect antibodies in the presence of the drug. Most of the drug-tolerant assays make use of acid to dissociate drug-anti-drug complex, but harsh conditions can deform antibodies causing false positives. Therefore, only mild acidification should be performed. The bridging assay, in which the drug is used both to capture and detect anti-drug antibody, is widely used but cannot detect ADA in the presence of the drug. However, a recent paper demonstrated that the protocol of the bridging assay can be adapted easily through 2 pre-treatments steps increasing drug tolerance without causing false positives [16]. A third hurdle was the lack of standardization of the calibrator between the different assays. While in the TDM assays, drug itself is used as calibrator, anti-drug antibody assays use no or an arbitrary calibrator. The availability of a universal calibrator could greatly enhance the comparison between different assays. The Leuven group has generated monoclonal antibodies that can be used in different assay formats such as cell-based assays and ELISA and in both drug-sensitive as well as drug-tolerant assays for infliximab, adalimumab and golimumab [6, 42, 43]. A monoclonal antibody has the advantage of continuous production and perpetual features. The landmark TAXIT trial used a first-generation bridging assay with a polyclonal antibody as calibrator and a cut-off value of 8 µg/ml ATI to exclude patients from randomization [4]. In the meantime, this assay has been optimized to increase sensitivity and reduce aspecific binding and it uses the monoclonal antibody MA-IFX10F9 as calibrator. ROC analysis revealed that 8 µg/ml polyclonal antibody titer corresponds with 400 ng/ml MA-IFX10F9 equivalents (unpublished results). Treatment efficacy can be increased by dose-intensifying patients with low or transient ADA and by switching patients with persistent ADA to biologicals within- or out-of-class (fig. 2).

Conclusion

The advent of biological therapies raised significant pharmaco-economic concerns because the cost of biological treatment is much higher than the cost of conventional treatments, typically in the range of €10,000–20,000 per patient per year. Although biologicals are highly expensive, they are vital for patients unresponsive to initial treatments and can prevent consequences of inadequate treatment regimens, such as invasive surgery or relapse, which often needs hospitalization. Moreover, indirect costs, such as loss of productivity due to unemployment

and missed days of work of patients and caregivers, represent up to twice the direct healthcare costs. This means that, although the introduction of biologicals induced an increase of healthcare expenses for drug therapy, it also proved to reduce complications associated with disease progression, hospitalizations and surgical interventions. A ‘treat-to-target’ strategy based on regular assessment of both disease activity and drug concentrations by objective measures and subsequent adjustment of treatments is a new paradigm for the management of chronic inflammatory diseases, which will avoid the unnecessary expenditure of money due to inadequate drug use. Moreover, the increased knowledge on immunogenicity of biosimilars will enhance the acceptance of biosimilars in clinical practice. Since several infliximab assays have demonstrated equal reactivity with Remsima® and Inflectra® [34–36], there is a need to conduct TDM with biosimilars. Assays should come at a reasonable price, should be easy to perform and preferably allow one sample at the time of analysis with a short time-to-result. The availability of biosimilars and assays to monitor biosimilar concentrations will allow the implementation of both in daily clinical practice.

Disclosure Statement and Source of Funding

A. Gils Lecture fee(s): MSD, Janssen Biologicals, Abbvie, Pfizer, Takeda. Consultancy: UCB. Conflict with: license of infliximab, anti-infliximab and adalimumab ELISA from Institution to apDia and with lateral flow infliximab to R-Biopharm AG. Institution received Investigator-Initiated Research Grants from Pfizer.

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